Modelling the Role of Amelioration and Drug Lords on Drug Epidemics and the Impact of Substance Abuse on the Dynamics of HIV/AIDS

by

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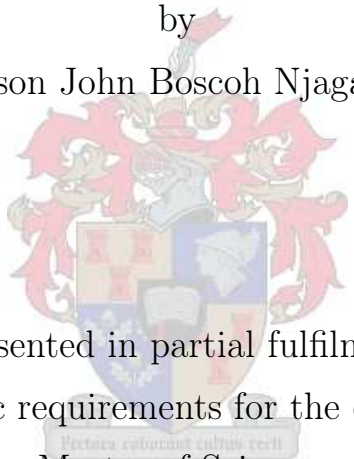

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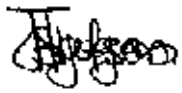

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Abstract

Substance abuse is an imminent danger on the health of both substance users and non-users. In general, abuse of psychoactive substances is associated with high risk behaviour, mortality and morbidity. The drug use cycle involves inextricably intertwined variants such as production, trading and usage of both licit and illicit addictive substances. The dynamics of substance use involve initiation, addiction, rehabilitation/treatment and quitting/recovery. In response to supply and abuse of monster drugs, control strategies such as law enforcement and rehabilitation have been stepped up to reduce access to drugs by targeting drug kingpins and harm reduction respectively. In this thesis, we model the factors affecting the prevalence of substance abuse, the effect of drug lords on the prevalence of substance abuse, and the impact of substance abuse on the prevalence of HIV/AIDS. We formulate mathematical models based on systems of autonomous differential equations describing the dynamics of the sub- populations involved in the drug using cycle. We examine the effects of amelioration, rehabilitation/treatment and re- initiation on the prevalence of substance abuse. Our results suggest that, recruitment into rehabilitation and amelioration in the presence of quitting for light users reduce the prevalence of substance abuse; re-initiation and amelioration without quitting for light users increase the prevalence of substance abuse. Our assessment of the impact of drug lords and the effect of law enforcement on drug epidemics shows that, the presence of drug lords seriously constraints the efforts to reduce substance abuse since they increase access to drugs. However, law enforcement if stepped up in response to the population of drug lords, greatly reduces the prevalence of substance abuse. Given the associated influence of drugs on high risky behaviour, as a cofactor for sexually transmitted infections, we assess the influence of substance abuse on the prevalence of Human Immunodeficiency Virus (HIV). Our results show that dissemination of information regarding HIV and drug use reduces HIV prevalence whereas, there is faster spread of the epidemic and high prevalence with increased sexual contact .

Opsomming

Dwelmmisbruik is 'n dreigende gevaar vir die gesondheid van beide dwelm gebruikers en nie-gebruikers. In die algemeen, word die misbruik van psigoaktiewe dwelms verbind met hoë risiko gedrag, mortaliteit en morbiditeit. Die dwelmgebruikskringloop behels onlosmaaklik vervlegde variante soos vervaardiging, handel en gebruik van beide wettige en onwettige verslawende middels. Die dinamika van dwelms behels aanvang, verslawing, rehabilitasie/behandeling en staking/herstel. In reaksie op die misbruik en verskaffing van monster dwelms, is beheer strategieë soos wetstoepassing en rehabilitasie verskerp, om die toegang tot dwelms te verminder, deur onderskeidelik te fokus op dwelmspilfigure en skadebeperking. Die belangrikste doel van hierdie verhandeling is om die faktore te modelleer wat die voorkoms van dwelmmisbruik beïnvloed, die uitwerking van dwelmbase op die voorkoms van dwelmmisbruik, en die trefkrag van dwelmmisbruik op die voorkoms van MIV / VIGS. Ons formuleer wiskundige modelle gegrond op stelsels van outonome differensiaalvergelykings, wat die dinamika beskryf van die sub-bevolkinge wat in die dwelmgebruikskringloop betrokke is. Ons ondersoek die effekte van verbetering, rehabilitasie/behandeling en heraanvang op die voorkoms van dwelmmisbruik. Ons resultate dui dat, werwing tot rehabilitasie en verbetering in die teenwoordigheid van stakende tydelike verbruikers, die voorkoms van dwelmmisbruik verminder; heraanvang en verbetering sonder dat tydelike verbruikers staak, verhoog die voorkoms van dwelmmisbruik. Ons raming van die invloed van dwelmbase en die uitwerking van wetstoepassing op dwelm-epidemies toon dat, die teenwoordigheid van dwelmbase belemmer grotendeels die pogings om dwelmmisbruik te verminder, aangesien hulle toegang tot dwelms verhoog. Nietemin, as die wetstoepassing verskerp word in reaksie op die dwelmbaasbevolking, word die voorkoms van dwelmmisbruik aansienlik verminder. Gegewe die gepaardgaande invloed van dwelms op hoë risiko gedrag as 'n kofaktor vir seksueel oordraagbare infeksies, beraam ons die invloed van dwelmmisbruik op die voorkoms van die Menslike Immunogebreksvirus (MIV). Ons resultate toon dat inligtingverspreiding rakende MIV en dwelmgebruik, MIV-voorkoms verlaag, terwyl daar 'n vinniger verspreiding van die epidemie en hoë voorkoms is, met verhoogde seksuele kontak.

Dedications

To my beloved Mum, Redemptor Kulabirawo and my siblings Mutebi Yuda, Kyalisiima Mary, Kobusingye Margaret, Kyakuwa Damascius and Kemugisha Pauline.

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Chapter 1

Introduction

1.1 Substance Abuse

Substance/drug abuse can be viewed as overindulgence in or dependence on a substance, drug or other chemical leading to effects that are injurious to the individual's physical, social, psychological and mental health and or the welfare of others. Most of the substances abused are psychoactive substances that lead to dependence syndrome when used.

Definition 1.1.1. *Dependence is defined as, "a cluster of cognitive, behavioural, and physiological symptoms indicating that the individual continues the use of the substance despite significant substance abuse related problems" [106].*

Substances abused include both licit (not prohibited by law) and illicit (prohibited by law) drugs. They can be classified into different classes depending on the level of abuse and the interest of the classifying organisation. In the case of South Africa [73], substances abused have been classified into those which are heavily abused, those moderately abused and those that are less frequently abused. The heavily abused substances include; alcohol (in all its forms), dagga (cannabis), cigarettes, dagga and mandrax combined, even though sometimes mandrax (methaqualone) is used on its own. Others in the same category include *prescription drugs* such as slimming tablets, tranquillisers and cough mixtures. Moderately abused substances include; cocaine (cocaine powder), crack- cocaine, heroin, speed, lysergic acid diethylamide (LSD), hashish, and Ecstasy MDMA. Also in this category is methamphetamine which is highly abused in the Western Cape province of South

Africa. Explicit information about health effects, behaviour, law and treatment program of Methamphetamine is provided in [62]. The least abused substances include; opium, Rohypnol, ketamine and wellconal.

In the USA, different bodies have classified drugs and the drug abuse disorders into different classes. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) divided the drugs and related disorders into 13 classes based on the drugs abused such as alcohol, sedatives, hypnotic or anxiolytic drugs, amphetamines, cocaine, caffeine, cannabis, hallucinogens (such as LSD) nicotine, opioid, phencyclidine (phenylcyclohexylpiperidine PCP) . Other bodies classify drugs as follows; the Diagnostic and Statistical Manual of the American Psychiatric Association, 13 categories, U.S DEA's and Coast Guard Scheme, 6 categories, Julien Biomedical-Type Scheme into 9 categories, Sussman and Ames Health Promotion Subjective-Behaviour Scheme into 8 categories [87]. We note that, even though the classification of substances may differ depending on the classifying body, the substances abused and the resulting effects are the same.

Drug addiction is a brain disease with well recognised cognitive, behavioural and physiological characteristics that contribute to compulsive and continued use of drugs despite the harmful consequences. The fact that recovery from drug addiction takes time, and addicts are at a high risk of relapse, effective rehabilitation programmes are not only required but also must last long enough to produce stable behavioural change and maintain abstinence over time. Scientist have also found that chronic drug abuse alters the brain's anatomy and chemistry and that these changes last for months or years after the individual has stopped using drugs. The major example was published by Wolkow et al. [102] on the lasting changes in the brain and the heart caused by addiction, see Figure 1.1.

The justification of the perplexing and continued abuse of drugs spans basic neurobiological, physiological, social and environmental factors. According to [102], repeated use of drugs changes how the brain functions, and affects the natural inhibition and reward centres of the brain. As a consequence, this results in transition from voluntary to adverse social, health or legal consequences. Although relapse may be largely due to withdraw symptoms and stress, craving for drugs may also be as a result of "spontaneous recovery" triggered by contact with people, places, and things associated with prior drug use.

In-spite of the continued warnings about the drug dependence and health problems asso-

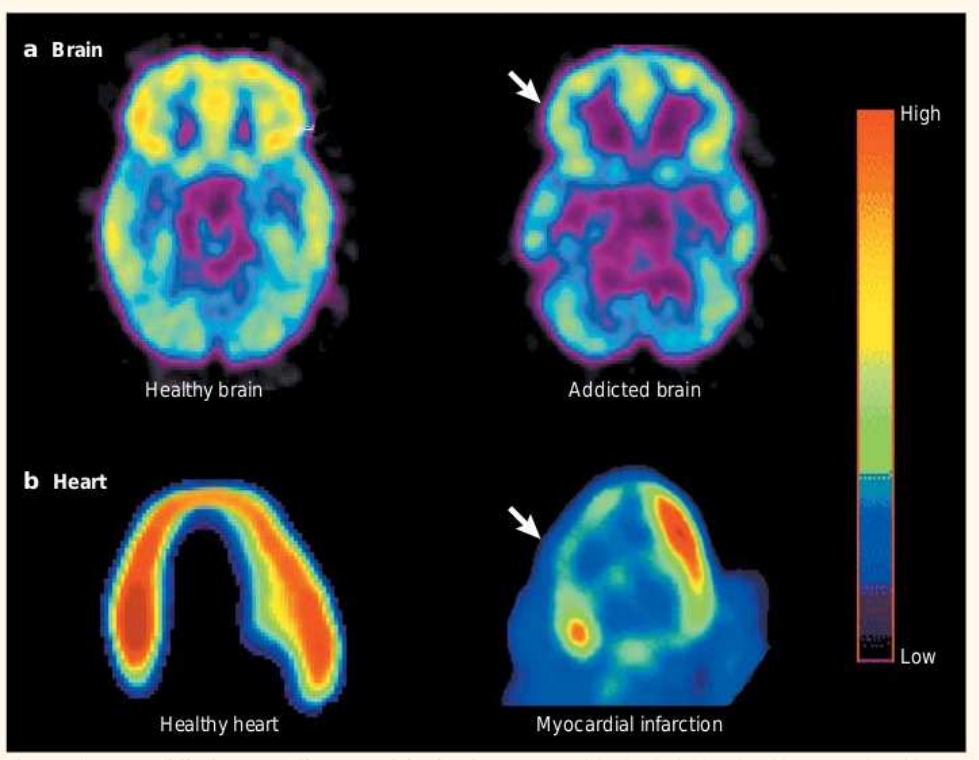


Figure 1.1. Source [102]: Images of the brain (a) in a healthy control and in an individual addicted to a drug, and parallel images of the heart (b) in a healthy control and in an individual with a myocardial infarction. Observe the decreased glucose metabolism in the orbital frontal Cortex (OFC),(arrow) of the addicted person and a decreased metabolism in the myocardial tissue (arrow) in the person with myocardial infarct. Damage of the OFC results in improper inhibitory control and compulsive behaviour, and damage of the myocardium in improper blood circulation.[For the interpretation of this figure with regard to colour, the reader is referred to the electronic version]

ciated with drugs, substance abuse has remained more or less equally prevalent. There are five principle conditions on which large spread, expansion and popularity of a given drug or set of drugs rests. According to Lloyd D Johnston [54], these include; awareness to the drug by potential users, access to the drugs, motivation to use the drugs, reassurance and willingness to violate social norms. All these factors are important not only for the popularity of the drug but also the expansion of the epidemic. When the population becomes aware of existence of the drug and its psychoactive potential, they can entertain the idea of using it. For most of the communicable diseases some individuals become aware of the risk of becoming infected and may choose either to take action or not [47]. This similar attitude is exhibited by drug users. By awareness to drugs, we refer to the population

having vivid knowledge about the merits and demerits of using a particular psychoactive substance. This may not be the case as some people use the drugs thinking that they will get better and end up getting addicted. The media undoubtedly plays a significant role in spreading the awareness of a particular drug throughout the population [54], and the same way reducing the prevalence of an epidemic [20], by encouraging behavioural change. Important evident case of awareness to substances can be confirmed from the many radio and television advertisements of cigarettes, and alcoholic products/brands such as Castle lager, Black label, Strong bow, Heinken, Bell, Carlsberg, Namaqua among others. Often times such advertisements completely outnumber the educational and sensitization programs. There is also a wide distribution of shebeens, wine testing places, and liquor shops most especially in Stellenbosch/western Cape. All these contribute to the population's access to the products as well as increasing awareness to the advertised products.

(a) (b)

Figure 1.2. Some selected brands of alcoholic products and wines commonly advertised

We note that, drug using career spreads faster when there is access to drugs and potential users are motivated by the psychoactive reassurances of the drug. It is believed that awareness without access can not result into use although increased access can result in awareness. For psychotherapeutic substances, there is easy accessibility due to their being widespread due to commercial distribution. In the same line, when the demand for psychotherapeutic drugs surpasses the amount that can be supplied from legitimate routes, then illegal importation or manufacture from clandestine laboratories may evolve to meet the demands. The main motivation for consuming drugs by the young stars has a lot

to do with psychological copying and conformity to the "group" most especially if social networking entails membership and conformity to a particular clique. Social modelling is cited as one of the most powerful mechanisms through which interest and motivation to use drugs is aroused. The strongest association found is a smoking area where a child raised by smoking parents and whose older siblings smoke becomes a smoker. Therefore, the modelling comes not only from friends but also others in one's most immediate role set, media and complete strangers. When the potential users observe the benefit of using a particular drug outweighing the cost of using the drug and the adverse effect, then re-assurance has been obtained. It can also be obtained through a variety of ways including assertion by others in one's immediate environment.

Substance abuse is associated with many dangers including the less well known such as holoprosencephaly (HPE) in fatal alcohol syndrome and leukoencephalopathy which is associated with inhaled heroin [9]. In this thesis, we detail some of the effects of drugs on the brain, some effects on the neuronal pathways and the resulting damage that can lead to disruption of cognitive and motor functions. The challenges are briefly organised in accordance with specific drugs and we concentrate more on the highly prevalent drugs including injectable drugs. The drugs have different modes of administration which include smoking, snorting (snuffing), oral ingestion and others are intravenously administered. The mode of administration determines the rate at which optimal levels of the drug in blood are reached [45] and the many harms including Chronic Obstructive Pulmonary Disease (COPD), Pulmonary edema, pulmonary hypertension, associated with abusing drugs [9, 40, 45]. The doctrine of types and nature of drug use involves recreational settings, society, family life experiences and psychiatric disorders.

1.1.1 Alcohol

Intoxication with alcohol to levels of over 0.1 percent/ml of blood has a significant fatality rate. Such a concentration impairs psycho-motor skills, causing errors in judgement, dis-orientation and hyperthermia [9]. As a result many accidents arise due impaired divided attention most especially in activities which require concentration such as driving and cycling, water sports and swimming, diving and boating accidents due aggravated spinal cord injuries and failure of the intoxicated individual to hold his breath. It is also impor-

tant to note the exasperating effects of intoxication on the central nervous system such as cerebral edema as a result of lipid peroxidation [21], association with low bone density (osteopenia) and skeletal disorder. Alcoholics often have deficiencies in minerals such as calcium, phosphate and magnesium [8, 44, 51, 89], as well as vitamin D which is vital for absorption of calcium from the intestinal system. Alcohol abuse has long been associated with impotence, sterility, testicular atrophy [99] and low testosterone [90] in men and early onset of menopause, miscarriage, impaired fertility and low birth weights among others in women. Excessive consumption of alcohol affects induction of polyamines [48] which regulate deoxyribonucleic acid (DNA) synthesis which reduces cell protein and DNA synthesis in normal osteoblasts [18, 28]. Alcohol has also been associated with cancers, gastric and ulcer disease, increased risk for colon cancer [32, 33], pancreatitis and liver cirrhosis which is the most serious damage to the liver. This impairs functioning of the liver leading to primary hepatic encephalopathy, a brain disorder characterised by altered psycho-motor, intellectual and behavioural functioning [9]. Chronic alcohol levels deplete hepatic levels of vitamins A and E antioxidants.

Cardiovascular disease has claimed lives of many people worldwide and the total alcohol consumed in a life span is directly associated with heart damage. The major condition is known as alcoholic cardiomyopathy characterised by deterioration of muscles of the heart. This is the major cause of heart failure and death [67, 68]. Other cases include hypertension associated with the action of alcohol on the Automatic Nervous System (ANS). This leads to release of stress hormones adrenaline and norepinephrine which constrict the blood vessels increasing blood pressure [9], increased ischemic and hemorrhagic strokes.

Although the relationship between alcohol consumption and subsequent sexual behaviour is not well understood, it is strong. For men arousal can be enhanced by mere expectancy that drinking has occurred. Alcohol is believed to provoke and heighten sexual responsiveness [3, 12]. However, the link between alcohol and sexual stimuli is complex since it involves psychological and physiological processes. The intensity is inversely proportional to the increase in blood alcohol concentration (BAC) in a linear fashion [10, 25]. In women increase in BAC is associated with reduced sexual arousal [107] and increases the time required to attain orgasm [60]. This can encourage multiple sexual relations especially if one partner is sexually inept.

1.1.2 Cocaine

Cocaine is an alkaloid occurring naturally and can be obtained from the plant “Erythroxylon Coca L". It can also be chemically synthesised with cold aqueous succinaldehyde, and cold aqueous methylamine, hydrogen chloride and the potassium salt of acetone-carboxylic acid monomethylester [45]. It is used medically by otorhinolaryngologists and plastic surgeons as an epinephrine cocaine mixture. The different modes of administration of the drug determine the rate at which cocaine appears in blood stream. These modes of administration detailed here and the corresponding times at which optimal levels are reached are based on [45] as follows; (1) Chewing powdered coca leaves containing 17-48 mg of cocaine produces a peak plasma concentration of 11-149 ng/ml at 0.4-2 hours of administration. (2) Orally taken gelatin capsules (2 mg/kg), the plasma concentration can reach the peak of 104-424 ng’ml in 50–90 minutes. (3) Through intranasal route, plasma concentrations of cocaine are reached between 35-90 minutes after “snorting". (4) Intravenous administration results in the plasma peak concentration in about 5 minutes. (5) It can be administered through smoking. In the study that was conducted [45], 50 mg of cocaine were smoked and the peak plasma concentration of 203 ng/ml was reached in 5 minutes. Pharmacologically cocaine is associated with effects such as tachycardia, vasoconstriction, mydriasis and hyperthermia. As a result of central nervous system (CNS) stimulations, there is increased alertness, diminished appetite and increased energy. Cocaine also acts as a local anaesthetic because of its ability to block the sodium channels in neuronal cells.

1.1.3 Marijuana

Marijuana refers to the plant cannabis sativa in all its forms (seeds, resin extracts from the plant, salt, derivative or mixture) except the mature stalk [45]. A variety of names are being used to refer to the drug such as weed, dope, pot, mull and leaf. It is commercially cultivated for hemp production. The bulk of the commercially cultivated plant consists of stalks with very little foliage, except at the apex. In contrast, the wild plants and those cultivated illegally posses numerous branches and a variety of psychoactive ingredients are concentrated in the leaves and the flowering tops. By 1995, the number of natural compounds identified in cannabis sativa was 483, and recently 6 new compounds new flavanoids have been discovered [46]. Marijuana is an annual plant and is cultivated in most

parts of the world such as the Canadian-American border, primarily by Asian gangs [46], in South Africa [73], Australia among other countries. The major psychotic constituent of marijuana is delta-9-tetrahydocannabinol (THC). Its concentration in the plant varies from part to part. Marijuana is administered as follows [45]; (1) The major route is by self administration through smoking leaves rolled in form of a cigarette. However, up to 30% loss of THC is established due to pyrolysis and side stream smoke. Peak plasma THC concentration occur after 3-8 minutes and THC is present in the blood after the first puff from marijuana cigarette. When the drug is into the lungs (alveoli), there is rapid absorption into the blood stream and then transported to the brain. (2) When orally ingested, THC is 90 to 95% absorbed even though the oral route results in lower peak plasma concentrations of THC occurring at a later time. (3) Intravenous administration of 4 to 5 mg results into peak plasma concentrations of THC occurring in about 30 minutes.

Marijuana may produce a variety of effects such as sedation, euphoria, hallucinations, temporal distortion and delusion among others [45]. THC exerts effects on prostaglandin synthesis, DNA, RNA and protein metabolism. There are two cannabinoid receptors-CB1 and CB2 which are primary targets of endogenous cannabinoids (endocannabinoids). CB1 receptor is found in the brain while CB2 receptor is found in the immune tissues e.g spleen, thymus and tonsils. Therefore, marijuana not only works as a psychoactive substance but also affects the immune response.

1.1.4 Heroin and Whoonga

Heroin is a well known addictive substance. Information about the modes of administration and the related psychoactive and behavioural effects have been detailed in [45, 93].In the case of South Africa, heroin has not gained much popularity because of the stigma against injecting drugs. Therefore, in the areas where it is prevalent, it is mainly smoked. The drug using population has been rocked by a new mainly smoked highly addictive drug (Whoonga), a derivative of heroin, that has come up in the townships surrounding Durban-South Africa. Whoonga is a mixture of various substance which include heroin, HIV medication (Anti-retrovirals), rat poison and detergents among others [86, 93]. The users become anxious and aggressive in addition to suffering from various pains including back pain, excessive sweating, headache, and potentially deadly stomach cramps. Such

symptoms are believed to be cured by a single dose, every time they arise. This leads to addiction and users resort to committing crimes to feed their addiction.

1.1.5 Substance Abuse and the Immune System

Drugs such as cocaine, marijuana, methamphetamine, heroin and nicotine are known to weaken and suppress immune function [104]. The suppression of immune function is due to immunomodulation and this increases susceptibility to infections and has a direct effect on pathogenesis of infectious diseases. Immunomodulation may be directly due to the toxic agents contained in the substances or indirectly due to the effects on the neuroendocrine system [29]. Illicit drugs especially the injection drugs are associated with increased transmission of HIV, hepatitis B and C together with other infectious diseases [22, 50, 88] through the central nervous system and brain function [30, 104]. According to [29, 34], opiates such as morphine and heroin have been associated with a decrease in the T-helper/cytotoxic T-cell (CD4/CD8) ratio in addicts.

1.2 Drug Abuse Versus Behaviour

Drugs affect important parts of the brain, necessary to control life-sustaining functions and can influence compulsive drug abuse that marks addiction. The main parts affected by addiction to drugs include [87]:

1. The brain stem; which controls basic life critical functions such as heart rate, breathing and sleeping.

2. The limbic system which links the brain structures necessary to control and regulate pleasurable feelings. Pleasure motivates us to repeat behaviours that may be critical to our existence. The limbic system is activated when we perform the critical activities and also by drugs of abuse.

3. The cerebral cortex; the frontal cortex is the center for thinking in the brain which powers our ability to think rationally, solve problems, plan and make decisions. If the frontal cortex is affected by stimulation due to drugs, rational thinking is impaired.

Substances like marijuana and heroin can activate neurons since their chemical structure mimics that of neurotransmitters although not exactly in the same way as the neurotransmitters. Amphetamine and cocaine can disrupt communication channels [101] through amplification of the messages sent to the brain. Direct or indirect stimulation with dopamine produces euphoric effects which teach people to repeat life sustaining behaviour sought by drug abusers without thinking about the outcomes. Drug abuse erodes a person's ability to make rational decisions and one's self control while amplifying the desire to take drugs. Information about addiction to crank cocaine indicates that addiction can further increase users' exposure to unprotected sex as a means to obtain drugs. It is rational to believe that such behaviour can cut across most of the psychoactive substances. Therefore, physiological consequences of addiction may alter susceptibility to infection and interact with HIV treatment drugs.

1.2.1 Substance Abuse and HIV/AIDS

At the end of 2008, an estimated 33.4 million people in the world [31.1 million-35.8 million] were living with HIV/AIDS. There was an estimated 2.0 million [1.7 million-2.4 million] deaths due to the killer epidemic. sub-Saharan Africa remains the most heavily affected with an estimated 22.4 million people living with HIV/AIDS and the same region accounted for 71% of all recorded new infections in 2008 [95]. Most countries have reported HIV infection in most of their administrative regions with an estimated 6.85 million people living with HIV/AIDS in South Africa [95]. The major modes of transmission include sexual contacts among homosexual and bisexual men, in the heterosexual population with an infected person and mother to child transmission. The virus can be introduced into the blood stream through contaminated needles of transfusion of contaminated blood as well as perinatal transmission. According to [11], the AIDS incidence in the United States is highest among homosexual or bisexual men and intravenous drug users. Although the HIV virus is spread mainly through sexual contact with infected people, it became clear early in the epidemic that the virus was being spread through other means such as sharing injection equipment mainly by injecting drug users. It has been observed that, the future course of HIV pandemic in the most populous countries will be determined by emerging epidemics [94]. In this report a detailed description of HIV prevalence among IDUs and sex workers (with a big problem in brothels) in some selected sites in Indonesia is given,

with a close link between HIV prevalence and injectable drug use. In these most populous countries, HIV transmission has been on an increase recently . An estimate of 15.9 million people were IDUs of whom 3 million may be living with HIV [98]. According to [69], drug addiction plays a significant but less recognised role in the transmission of HIV. Intoxication by drugs alters the users' mental status and judgement, which increases the probability of engaging in high risk behaviour which include.

- Unprotected sexual contact among the intoxicated drug users and, or sexual partners. This includes improper usage of condoms when intoxicated.
- Engaging in commercial sex work.
- Acquisition of multiple sexual partners and intensification the drug users' sexual desire catalysed by stimulants and psychoactive substances.

Drug use and has not only been problematic in the Western world, but also on the African continent. In Table 1.1, we give figures of some selected countries showing the association between Drug use and HIV/AIDS prevalence.

	Estimated no. of IDUs	Injecting prevalence among drug users	Injecting risk (% sharing equipment)	Unsafe sex practices (% multiple partners and/or unprotected sex)	HIV prevalence among the general population (%)	HIV prevalence among IDUs (%)
Nigeria		3–45	11–40	38–40	5	9 in Lagos, 44 among female IDUs
Kenya	130 748	23; 50 in Malindi	27.5	30	6	23–53
Tanzania	2000–2500 in Dar es Salaam	40 on Zanzibar	33 in Dar es Salaam; 46 on Zanzibar	68–85	10	29–42 in Dar es Salaam; 65 among female IDUs
Mauritius	17 000	1.5 among general population; 50 of prisoners	23–30	88	1.8	
South Africa	260 000		86	65	15–39	19–35

Table 1.1. Source [49]: Drug-related HIV risk behaviour and HIV prevalence per country

The faster growth in the incidence of HIV in many regions has been attributed to emerging epidemics among injecting drug users (IDUs) in Russia, India and China [35]. In China

IDUs account for 60–70% of all reported infections, although the importance of heterosexual transmission has increased to 7% [35]. In India, the majority (85%) of new infections are due to heterosexual transmission, particularly among sex workers (SWs), and the sexual contacts with their clients. However, in north-east India and major cites such as Delhi, Chennai and Mumbai, injecting drug use is the major source of new infections [94].

1.3 Perception and Drug Use

When more individuals perceive a drug as detrimental to their health, the consumption and prevalence tend to reduce. The major example justifying this inverse relationship between awareness and prevalence is given in the research conducted over a period of 28 years. In this research, the prevalence rate for marijuana use over a twelve months period and the perception of marijuana as a dangerous drug in 12^{th} graders (18-19 years old) from 1975-2003 in the USA was considered. The data is provided in [43] and the plot of which is indicated in Figure 1.3, is similar to the one obtained in [102].

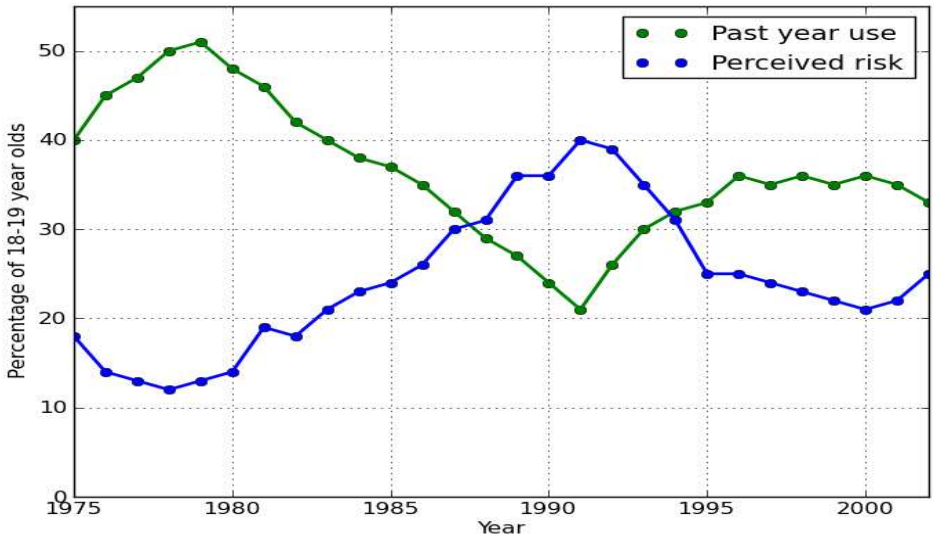


Figure 1.3. Shows the observed past year use of marijuana with perceived risk of Marijuana as a harmful substance.

We observe from Figure 1.3 that, when teenagers perceived marijuana as dangerous, the

prevalence of drug use was low. This is true for most epidemics in that, people usually change behaviour on perceiving the risk of infection.

1.4 Project Motivation and Objectives of the Study

1.4.1 Motivation

Substance abuse epidemics have very complex dynamics ranging from the change in the number of drug users, the type of drugs an individual consumes as their primary or secondary drugs, and the amount of a particular drug an individual may need to quench the addiction. Substance abuse imposes heavy budgetary constraints in many countries. For example it costs South Africa over R20 billion annually [93], in the course of treating drug users, cracking down drug traffickers and in prevention and media campaigns. According to the United Nations Office on Drugs and Crime (UNODC), an estimated 155-250 million people in the world (3.5 to 5.7% of the population aged between 15 and 64) used illicit drugs at-least once in 2008. Cannabis users comprise the largest number (129-190 million people) [98]. There is a likelihood that the number of drug users is under estimated since some people start abusing drugs at a much lower age. Here we cite an example of South Africa where Gautenge's youngest known drug dealer was the eight year old boy from Douglasdale [93]. The primary drugs of abuse among people who reported to treatment centres in Africa, Americas, Europe, Asia, Oceania are listed in [98] and these are associated with morbidity. The top abused illicit drugs are: Cannabis, in Africa and Oceania with an average (un weighted) consumption of 63.4% and 46.5% respectively, the sum of all cocaine in Americas 46.4%, opiates in Asia and Europe at 61.8% and 48.3% respectively [98]. On the other hand, it is claimed that cocaine and heroin are at the fore front among the abused illicit drugs in sub-Saharan Africa [42]. Since drug use is illegal, accurately predicting the population of drug users, estimating the associated budgetary constraints,and analysing the cost effectiveness of the control measures remain daunting task.
Mathematical models have become handy in predicting the drug use patterns, estimating the prevalence and consequently the population of drug users, and lastly analysing the factors that influence drug use patterns and predicting possible remedies to the epidemic.

1.4.2 Project Objectives

The main objective of this work is study the dynamics of substance abuse. In particular, to construct a useful mathematical model incorporating important macro-epidemiological parameters influencing the spread of the epidemic and possible control strategies. The objectives of the study are;

1. To give a general understanding of substance abuse, modes of administration of drugs, factors influencing the spread of the epidemic and the morbidity associated with substance abuse.
2. To study the variation of the population of substance users and the impact of vital parameters such as rehabilitation, amelioration and re-initiation/relapse on the prevalence of substance abuse.
3. To investigate through scenario analysis and simulation procedures, the influence of drug lords interacting with the susceptible population, law enforcement targeting drug lords, on the prevalence of substance abuse.
4. To investigate the potential impact of substance abuse on the prevalence of HIV/AIDS.

1.5 Mathematical Preliminaries

1.5.1 Definitions and Notations and Propositions

For the definitions, propositions and lemmas given in this subsection, we closely follow work in [53, 76]. Let U be an open set of $\mathbb{R}^n$. A function $f : U \to \mathbb{R}^n$ is said to be a C^r map for $0 \leq r \leq \infty$ if all partial derivatives up through order r exist for all points of U and are continuous. In the extreme case C^0 means that f is continuous and C^∞ means that all partial derivatives of all order exist and are continuous on U.

Definition 1.5.1. *[53] A function $f : U \to \mathbb{R}^n$ is a C^r map if $f_i := \pi_i f$ is C^r for $i = 1, 2, \ldots n$ where $\pi_i : \mathbb{R}^n \to \mathbb{R}$ is the i^{th} projection map defined by $\pi_i(x_i, \ldots, x_n) = x_i$.*

Let $x_i \longmapsto f(x_i)$ be a map from an open subset $D_1 \subset \mathbb{R}^n$ to $\mathbb{R}^n$ such that each solution $x(t)$ to the system of differential equations

$$\dot{x_i} = f(x_i) \tag{1.1}$$

is uniquely determined by its initial conditions $x_i(0) = x_{i0}$, and denote the solution by $x(t, x_0)$. Let the nonlinear system (1.1) have a linear form given by

$$\dot{x_i} = Ax, \tag{1.2}$$

with $A = Df(x_0)$.

Proposition 1.5.1. *Let U be a non-empty open subset of $\mathbb{R}^n$ and let $f : U \to \mathbb{R}^n$ be a C^1 map. Then f is differentiable at all $x \in U$ and*

$$Df = Jf := \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{bmatrix}.$$

Clearly, $Df(x) = Jf(x) : \mathbb{R}^n \to \mathbb{R}^n$, where the entries of the Jacobian matrix are evaluated at $x = (x_i, \ldots, x_n)$. Let also $x^* \in \mathbf{E}$ be an equilibrium point of (1.1).

Definition 1.5.2. *A point $x^* \subset \mathbb{R}^n$ is an equilibrium point of (1.1) if $f(x^*) = 0$. x^* is called a hyperbolic equilibrium point of (1.1) if non of the eigenvalues of the matrix $Df(x^*)$ has a zero real part.*

Definition 1.5.3. *x^* is said to be locally stable or simply stable if, for each neighbourhood U of x^*, there exists a neighbourhood V of x^* such that $x(t, v) \subset U$ for all $v \in V$ and for all $t > 0$.*

In other words, if x^* is a stable equilibrium point of (1.1), no eigenvalue of $Df(x^*)$ has a positive real part. In this case the solutions starting at nearby initial conditions, remain close to x^*. More precisely, x^* is stable if and only if for any $\varepsilon > 0$, there exists a corresponding number $\delta(\varepsilon) > 0$ such that

$$\|x(t_0) - x^*\| < \delta(\varepsilon) \quad \Longrightarrow \quad \|x(t) - x^*\| < \varepsilon$$

for all $t > t_0$.

In this case, x^* is said to attract points in a neighbourhood W if $x(t, x_0) \to x^*$ as $t \to \infty$ for each $x_0 \in W$. We also note that x^* may fail to be stable when it attracts points in the neighbourhood of W.

Definition 1.5.4. *If x^* is stable and attracts points in a bound set W, then the attraction is uniform with respect to $x_0 \in W$ and x is asymptotically stable.*

An equilibrium point x^* is asymptotically stable if there exists $\delta > 0$ such that

$$\|x(t_0) - x^*\| < \delta \quad \Longrightarrow \quad \lim_{t\to\infty} \|x(t) - x^*\| = 0.$$

That is, all solutions starting sufficiently close to x^* will converge to x^*. This can be summarized into the following lemma.

Lemma 1.5.1. *Let D_1 be an invariant space containing an open set $\mathbf{E}$. $x^* \in \mathbf{E}$ is asymptotically stable if it is stable and attracts the neighbourhood (all points in the basin of attraction) of $\mathbf{E} \in D_1$.*

Definition 1.5.5. *An equilibrium x^* is said to be globally asymptotically stable with respect to an open set $\mathbf{E}$ if it is asymptotically stable and its basin of attraction contains D_1*

The local stability of systems of differential equations describing the flow of epidemics is done using the linearisation method. this is motivated by Theorem 1.5.1

Theorem 1.5.1. *(Hartman-Grobman Theorem)[76]. let $\mathbf{E}$ be an open subset of $\mathbb{R}^n$ containing the origin, let $f \in C^1(\mathbf{E})$, and ϕ_t be the flow of the non-linear system (1.1). Suppose that $f(0) = 0$ and that the matrix $A = D(f(0))$ has no eigenvalue with zero real part, Then there exists a homeomorphism H of an open set U containing the origin onto an open set V containing the origin such that for each $x^* \in U$, there is an open interval $I_0 \subset \mathbb{R}$ containing zero such that for all $x^* \in U$ and $t \in I_0$*

$$H \circ \phi_t(x^*) = e^{At} H(x^*) \tag{1.3}$$

that is H maps trajectories of (1.1) near the origin onto trajectories of (1.2) near the origin and preserves the parametrisation by time.

Thus the two autonomous systems are said to be topologically equivalent. For the outline of the proof of Theorem 1.5.1, see [76]. We use the linearisation method to prove local stability of the system. On the other, hand if the equilibrium point of $Df(x^*)$ is non-hyperbolic, then the linearisation process does not provide enough information about the stability of the equilibrium point. We then use the lyapunov function as described below.

Let the function V be a continuous function defined as $V : \mathbb{R}^n \to \mathbb{R}$. If V satisfies the hypotheses in Theorem 1.5.2, then it is a Lyapunov function

Theorem 1.5.2. *Let* $\mathbf{E}$ *be an open subset of* $\mathbb{R}^n$ *containing* x^*. *Suppose that* $f \in C^1(\mathbf{E})$ *and that* $f(x^*) = 0$. *Suppose further that there exists a real valued function* $V \in C^1(\mathbf{E})$ *satisfying* $V(x^*) = 0$ *and* $V(x) > 0$ *if* $x \neq x^*$. *Then*

(a) if $\dot{V}(x) \leq 0$ *for all* $x \in \mathbf{E}$, x^* *is stable;*

(b) if $\dot{V}(x) < 0$ *for all* $x \in \mathbf{E} \setminus \{x^*\}$, x^* *is asymptotically stable;*

(c) if $\dot{V}(x) > 0$ *for some* $x \in \mathbf{E} \setminus \{x^*\}$, x^* *is unstable.*

A lyapunov function is challenging to construct, but once one is constructed and satisfies the first two conditions of Theorem 1.5.2, then the associated steady state of the dynamical system is stable. In addition, lyapunov like functions have been used to prove persistence and permanence of the population in both epidemiological and ecological models. An example of this application to prove persistence of solution is illustrated with the model in section 3.5.

1.6 Outline of the Thesis

In Chapter 1 a general background of substance abuse is provided, citing the factors influencing the spread of the epidemic, major substances abused, modes of administration and the related times at which peak plasma concentrations are reached. It is in this chapter where we gave the close association between substance abuse and behaviour and consequently the spread of HIV/AIDS. We also indicated a number of medical complications which arise from using substances, the associated immune suppression, and alteration of functioning of natural killer cells. In this chapter we showed basing on the available research results that increased awareness of the risk of using substances results in decreased prevalence of such drug epidemics. Lastly, we gave some mathematical preliminary definitions and concepts needed in the later chapters. In Chapter 2, we review some studies done on modelling substance abuse and compartmentalisation of the "core" population. In Chapter 3, we formulate a deterministic drug using compartmental model incorporating

rehabilitation/treatment, amelioration and re-initiation into substance abuse as the sociological parameters and then analyse how each of these parameters influences the prevalence of substance abuse. In Chapter 4, we extend the model to incorporate the influence of drug lords as the leaders of the black market, and how law enforcement may impact the prevalence and incidence of substance abuse. In Chapter 5, we analyse the potential impact of drug abuse on the prevalence of HIV/AIDS and lastly, in Chapter 6, we present the general discussion and conclusion to the thesis and give commendations of possible improvement of the model to better understand drug epidemics and further research.

Chapter 2

Literature Review

2.1 Substance Abuse Models

The general ideas and techniques used in mathematical modelling of epidemics and infectious diseases begin with the disease statistics dating from Daniel Bernoulli's smallpox data of 1760. This resulted in description of simple deterministic and stochastic models in continuous and discrete time for epidemics occurring in homogeneous and non homogeneous populations. Both types of models (stochastic and deterministic) have a role to play in describing the spread of infections in small and large populations respectively. Interesting to note is that, a wide range of techniques for constructing and analysing epidemic models in human populations are now available, but mostly in the context of viral and bacterial diseases. The main interest of the modelling process is to fit realistic mathematical models to data, and use the models and data to; estimate the vital parameters driving the epidemic, devise necessary strategies for controlling the spread of epidemic and then advise policy makers and health practitioners on how to abate the epidemic burden.

Compartmental models have been used to analyse the dynamics of epidemics in the population, as well as describing and understanding the various aspects of substance abuse which include "measuring" of substance abuse prevalence and the response to drug use control interventions [80, 81]. In these compartmental models, the population is categorised into different sub-populations where members in the compartment are at the same level of infection (homogeneous) and the different compartments are heterogeneous. The general

population is classified into two categories; "movers" and "stayers" [80, 81] or "core" and "non core" group [71]. The movers/core group, form the major susceptible pool for drug epidemics. They can be initiated into drug use and they continue with the drug using career. The stayers/non-core group, is a group of individuals who are not prone to initiation into drug use due to their "circumspect" behaviour.

There has been growing interest in mathematical modelling of substance abuse dynamics. The reasons for this are; to understand the dynamics and evolution of the population of substance abusers, initiation into drug use, prevention and treatment strategies. The modelling approach is based on the evidence that drug use spreads as an infectious disease with the rate of occurrence of new cases depending on the number of drug users and the susceptible population [57, 81]. The main difference between drug users and the "infected" persons is a microbial process [57]. However, drug use being illegal, estimating the actual population of drug users is challenging as opposed to infectious diseases. In addition, the sociological parameters in the drug field may be area/country specific and may not be presumably the same in different countries as the case may be for infectious diseases [81]. In [5], analysis of drug use with optimal control of drug epidemics involving prevention and treatment was based on a first order ordinary difference equation model introduced by Everingham and Rydell [24] and described by Behrens et al. in [23]. In the model, initiation into drug use was made an endogenous function of prevalence as in [6], and involved a group of self initiated drug users referred to as "innovators". Since drug users do not behave as diseased individuals, distinguishing between light users and heavy users may be challenging. Everingham and Rydell (1994) [24], with their simple two-state Markov model of cocaine demand distinguished between "light users" and "heavy users" as a pioneering contribution of understanding drug policy. They classified individuals who reported using cocaine "at least weekly" as "heavy users" and those who consumed within the past year but less than weekly as "light users".

The simplest known epidemic model is the classical SI model, with only two compartments, the susceptible S and infected population I. Most epidemic models however, are built on the basis of the classical SIS and SIR models. One of the simplest models of substance abuse, inspired by the SIR model, was presented by Brandy benedict (2007)[7]. The model was presented under the acronym SAR, used for modelling alcoholism as a contagious condition. The model has three compartments: Susceptible (S), Alcoholics (A) and the

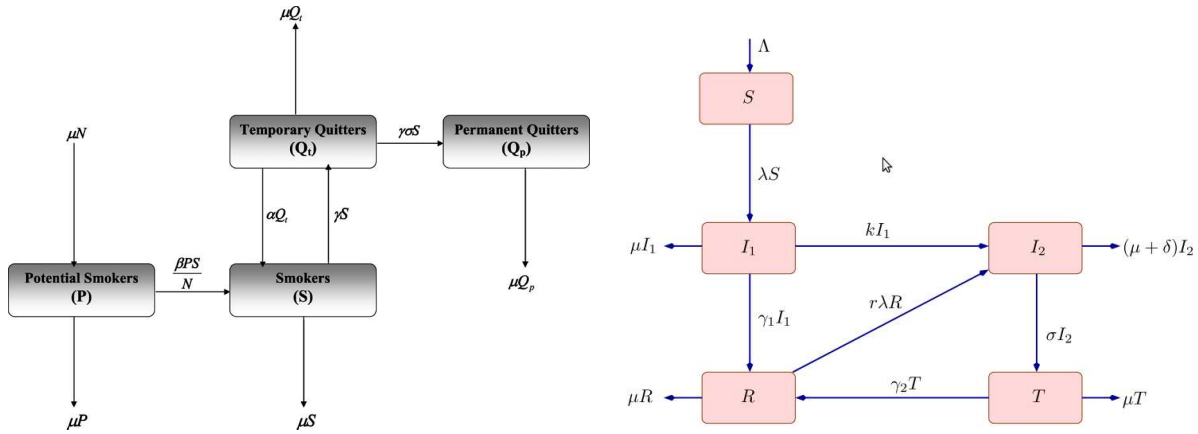
removed or recovered (R). Initiation into substance abuse is proportional to product of the number of susceptible individuals and the fraction (A/N) of the alcoholics in the population each susceptible individual encounters. In this model, all the alcoholics were classified to be in the same group irrespective of their level of alcohol usage. In this model still, no removal rate associated with alcohol abuse was accounted for. This may be lacking since heavy alcohol usage is associated with risky behaviour, morbidity and mortality.

Control of drugs has been a global agenda for more than a century now. Efforts have been directed towards prevention of initiation into drug use and rehabilitation of drug addicts. The effectiveness and efficiency of control efforts such as education and media campaigns in preventing initiation into drugs and accelerating quitting can not be easily quantified. The drug use trends can however be observed through routine data collection [20]. Mathematical models on substance abuse have been formulated and analyzed by a number of authors in recent years, see for instance [71, 72, 83, 105]. They have been insightful in the understanding of the dynamics of substance abuse, initiation into drug use, prevention and treatment strategies. The fact that drug users do not behave like diseased individuals, estimating the actual population of drug users may be challenging. Therefore, knowledge of the epidemiology of drug use patterns, social networks and the potential impact of drug epidemics is essential.

Two models on drug epidemics have been proposed recently. The first model was by White and Comiskey [105] on heroin epidemics. In their model, three classes of individuals were considered, namely, susceptibles, heroin users not on treatment and heroin users on treatment. A drug epidemic threshold, the basic reproduction ratio, was determined and the model analysis was based on the threshold parameter. Stabilities of the equilibria of the model in [105] were proved by Mulone and Straughan [64] under a realistic condition that the relapse rate of those in treatment returning to untreated drug use is greater than the prevalence rate of susceptibles becoming drug users. The model was extend in [71] to model methamphetamine abuse in Western Cape. In the extended model Figure 2.1(b), the class of drug users not on treatment was divided into classes of drug users who are allowed to pass through a period of concealed drug use at the beginning (light drug users) and hard drug users. The model allowed for quitting/recovery of those under treatment into a class of the recovered and a relapse for the recovered individuals. The model in [105], was also modified by Samanta [83], through the introduction of time dependent parameters, time

dependent total population size and distributed time delay.

A typical drug use cycle consists of being at risk, concealed drugs use soon after initiation, addiction, treatment, recovery and relapse, whose dynamics are not well understood. Unlike in [71, 83, 105], in addition to treatment- recovery-relapse cycle, we also assume an ameliorative process that considers the transfer of hard drug users, to light drug use and to being at risk again but not using drugs. The model assumes two processes of quitting drugs; firstly through rehabilitation and secondly through a systematic withdrawal process in which an individual moves from being a hard drug user, to a light user and to complete recovery. In [71, 83, 84, 105], the models assume that once an individual starts using drugs, they can not be susceptible or be at risk again. See the sample flow diagrams indicated in Figure 2.1. This assumption may not be realistic in our view.



(a) Source [84]: A flow chart of a smoking a epidemic model.

(b) Source [71]: A compartmental representation of the epidemic of methamphetamine use

Figure 2.1. Sample flow diagrams used in modelling substance abuse.

In the first phase of drug use, users can either stop using drugs, continue using drugs or die [81]. When they stop using drugs, they become susceptible again and if they continue using drugs they become addicts. We allow drug addicts to either revert to light drug use or to be recruited into rehabilitation programs.

In this thesis, we thus propose a mathematical model for a drug epidemic in which amelioration, treatment and relapse are considered with the aim of studying the global dynamics of the model. Sufficient conditions ensuring the existence and uniqueness of globally stable equilibria are derived using the direct Lyapunov method. Determining the global stability

of equilibria in models with several classes is not trivial. We analyse the global stability of the model formulated and give some numerical simulations. We then extend the model to incorporate the influence from drug lords in the initiation process and the impact of law enforcement on the prevalence of substance abuse. Finally, we use the first model, and involve the transition of drug users to HIV/AIDS seropositive state based on non-linear transmission due to their involvement in risky behaviour, and then analyse the impact of substance abuse on the prevalence of HIV/AIDS.

Chapter 3

Model with Amelioration

3.1 Introduction

Mathematical modelling in population biology, ecology and epidemiology has been developing for many years to monitor the evolution of human populations over time, water-borne and zoonotic infections, micro and macro-organism, chemostat and enzymatic reactions, cellular and metabolic pathways, tropical and many infectious disease among others. Behavioural driven epidemics such as substance abuse have been a menace to communities accounting for significant morbidity and mortality, but little research has been done to understand such epidemics. Drug epidemics drive many other epidemics especially, those involving heightened sexual arousal arising from consumption of psychoactive substances. In this chapter, we formulate a deterministic model for substance abuse dynamics inspired by the work done in [71, 84]. The purpose of our modelling work is to identify and quantify the contribution of some key parameters driving the epidemic. The following differentiate our model from the models presented in [71] and [84] as follows:

(i) We allow for amelioration of heavy drug users to the light drug using class and reversion/relapse of drug users under rehabilitation into heavy drug use, since rehabilitation may not be 100% effective and also due to withdrawal effects. Direct reversion for the rehabilitation class to heavy using class is because, the amount substance needed by relapsing individuals to feel "normal" is almost equal to their usage level.

(ii) We also consider quitting for light users since after initiation some individuals may not like the drug or change behaviour and quit. In the same way, heavy drug users on the road to recovery (ameliorating drug users), may quit slowly through light drug use but remain at risk of using drugs.

(iii) Unlike in [84], we include a drug related removal rate for heavy drug users used in [71]. We also account for an additional removal rate for drug users under rehabilitation.

3.2 Mathematical Model Formulation

The model analyses the dynamics of drug abuse in a heterogeneous population. The population is stratified into four classes: those at risk of using drugs (susceptible) denoted by S, light users L, heavy users H, and drug users on treatment T. The total variable population size at any time t is given by

$$N(t) = S(t) + L(t) + H(t) + T(t).$$

We assume that the individuals in each compartment are indistinguishable and there is homogeneous mixing. The model assumes that individuals join the susceptible population at a rate π through births and immigration. Susceptible individuals are initiated into drug use following interaction with individuals using drugs. We thus assume an initiation function that is analogous to the force of infection for epidemic models. In this case, the per capita contact rate β is a product of the effective number of contacts c, between drug users and the susceptible population, and the probability $\hat{\beta}$, that a contact results in initiation into drug use so that $\beta = c\hat{\beta}$. A fraction $Lf(N)$ of the contacts are with light users and the average number of relevant contacts of each individual with light users is $\beta Lf(N)$, where $f(N)$ is the density function. Also, $\eta_1\beta Hf(N)$ and $\eta_2\beta Tf(N)$ are the relevant contacts of each individual with a heavy user and a user under treatment respectively. The parameters η_1 and η_2 measure the relative ability to initiate new drug users for heavy users and those in treatment respectively when compared to light users. Assuming that the rate at which heavy users and those in treatment recruit initiates is lower than that of light users, we have $0 \leq \eta_1, \eta_2 < 1$. This is due to the fact that problematic drug use is associated with morbidity and this serves as "negative" advertisement. The total number relevant contacts

gives the initiation function using mass action incidence,

$$\Lambda = f(N)\beta\left(L + \eta_1 H + \eta_2 T\right). \tag{3.1}$$

Upon infection, a susceptible individual moves into the compartment of light users. The light use phase, represents initial phase of drug abuse and individuals can either stop, die or move to heavy drug use. It is at this stage that our model differs from a number of models on substance abuse. We argue that this approach is representative of drug use cycles. Heavy drug users can either revert to light drug use, die, join rehabilitation programmes or they are removed due to drug use related problems. Removal due to substance abuse related problems include incarceration and deaths directly caused by the use of drugs. This is of particular importance when one considers the fact that drug abuse often impairs judgement for drivers, increases the risk of contracting killer diseases such as HIV and often leads to violent crimes as addicts search for money to buy drug doses. Once in rehabilitation individuals can either have a relapse to hard drug use, quit permanently, die or they are also removed due to drug use related problems. The possible transitions of a drug user's career are represented by the schematic diagram, Figure 3.1.

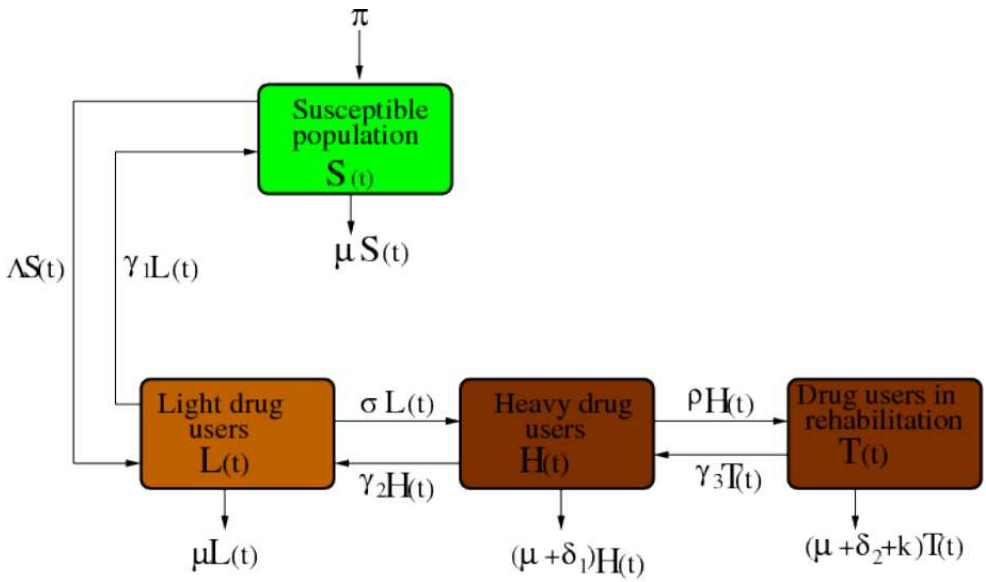


Figure 3.1. Model diagram indicating possible transitions in the drug using career

The model system of ordinary differential equations is given below;

$$\begin{aligned}
\frac{dS}{dt} &= \pi - \Lambda S - \mu S + \gamma_1 L, \\
\frac{dL}{dt} &= \Lambda S + \gamma_2 H - (\mu + \sigma + \gamma_1) L, \\
\frac{dH}{dt} &= \sigma L + \gamma_3 T - (\rho + \gamma_2 + \mu + \delta_1) H, \\
\frac{dT}{dt} &= \rho H - (\gamma_3 + k + \mu + \delta_2) T.
\end{aligned} \tag{3.2}$$

The descriptions of the parameters that describe the flow rates between compartments are given in Table. 3.1.

Table 3.1. Description of parameters used in the model.

Symbol	Description
β	The effective contact rate between drugs users and the susceptible population
η_1	The relative ability to initiate new drug users by heavy users
η_2	The relative ability to initiate new drug users by users in rehabilitation
π	Recruitment rate into the susceptible population
μ	Natural mortality rate of the population
σ	The mean rate at which light users escalate to heavy drug use
γ_1	The rate at which light users quit and become susceptible again
γ_2	The rate at which heavy drug users move back into light drug use
ρ	The rate at which heavy drug users are recruited into rehabilitation
γ_3	The rate at which those under rehabilitation relapse into heavy drug use
δ_1	Removal rate related to drug use for heavy drug users
δ_2	Removal rate related to drug use for users under rehabilitation
k	The mean rate at which those in rehabilitation quit permanently

3.2.1 The Incidence Function

The incidence function is density dependent. We assume that the density dependence of the incidence is described by the function $f(N)$. In this case the function class of interest is $f(N) = N^{-\alpha}$, where $\alpha \in \{0, 1\}$. In this set of α, the incidence term includes the two common forms; mass action or bilinear incidence when $(\alpha = 0)$ and standard incidence for $(\alpha = 1)$. The incidence term being density dependent, indeed our initiation function is given by $\Lambda = f(N)\beta(L + \eta_1 H + \eta_2 T)$.

We assume that the function $f(N)$ is continuous and its first derivative is continuous on $\mathbb{R}$. If $f(N)$ is C^1 for $N > 0$, then $f(N)$ satisfies the satisfies the following assumptions [37];

(P1) $f(N) > 0$,

(P2) $f^{'}(N) < 0$ and

(P3) $|Nf^{'}(N)| \leq f(N)$ for $N > 0$ only.

The assumptions that $f(N) > 0$ and $f^{'}(N) < 0$ are biologically motivated. As the total population increases, the probability of contact between the drug user and the susceptible individual decreases. Therefore, the force of infection is a decreasing function of N.

The third condition ensures the uniqueness of the endemic equilibrium when $R_0 > 1$, and global stability of the drug free steady state when $R_0 \leq 1$. The conditions imply that $Nf(N)$ is monotonically non-decreasing since

$$(Nf(N))^{'} = f(N) + Nf^{'}(N) \geq 0.$$

We now apply the conditions $(P1)-(P3)$ to the class of functions $f(N) = N^{-\alpha}$, $\alpha \in \{0, 1\}$. It can easily be shown that the class of functions $f(N) = N^{-\alpha}$, satisfies the conditions $(P1) - (P3)$, only for $\alpha = 1$. In our model therefore, we use the function $f(N) = N^{-1}$, thus the incidence function is based on standard incidence. In this case, we assume that a susceptible individual meets only a fraction of substance users as opposed to mass action incidence. The force of infection in this model is thus given by

$$\Lambda = \beta(L + \eta_1 H + \eta_2 T)/N.$$

3.2.2 Basic Properties

Positivity of Solutions

We now consider the positivity of system (3.2). We prove that all the state variables remain non-negative and the solutions of the system (3.2) with positive initial conditions will remain positive for all $t > 0$. We thus state the following lemma.

Lemma 3.2.1. *Given that the initial conditions of system (3.2) are* $S_0 > 0,\ L_0 > 0,\ H_0 > 0$ *and* $T_0 > 0$, *the solutions* $S(t)$, $L(t)$, $H(t)$, *and* $T(t)$ *are non-negative for all* $t > 0$.

Proof. Assume that

$$\hat{t} = \sup\{t > 0 : S > 0, L > 0, H > 0, T > 0\} \in [0, t].$$

Thus $\hat{t} > 0$, and it follows directly from the first equation of the system (3.2) that

$$\frac{dS}{dt} = \pi - (\mu + \Lambda)S.$$

We thus have

$$\frac{d}{dt}\left[S(t)\exp\left\{\mu t + \int_0^t \Lambda(s)ds\right\}\right] \geq \pi \exp\left[\mu t + \int_0^t \Lambda(s)ds\right].$$

Hence

$$S(\hat{t})\exp\left[\mu\hat{t} + \int_0^{\hat{t}} \Lambda(s)ds\right] S(\hat{t})\exp\left[\mu\hat{t} + \int_0^{\hat{t}} \Lambda(s)ds\right] - S(0) \geq \int_0^{\hat{t}} \pi \exp\left[\mu\hat{t} + \int_0^{\hat{t}} \Lambda(w)dw\right] d\hat{t},$$

so that

$$\begin{aligned} S(\hat{t}) \quad \geq \quad & S(0)\exp\left[-\left(\mu\hat{t} + \int_0^{\hat{t}} \Lambda(s)ds\right)\right] \\ & + \exp\left[-\left(\mu\hat{t} + \int_0^{\hat{t}} \Lambda(s)ds\right)\right]\left[\int_0^{\hat{t}} \pi \exp\left(\mu\hat{t} + \int_0^{\hat{t}} \Lambda(w)dw\right) d\hat{t}\right] > 0. \end{aligned}$$

From the second equation of (3.2),

$$\begin{aligned} \dot{L} &= \Lambda S + \gamma H - (\mu + \sigma + \gamma_1)L, \\ &\geq -(\mu + \sigma + \gamma_1)L, \\ \Rightarrow L &\geq L_0 e^{-(\mu+\sigma+\gamma_1)t} > 0. \end{aligned}$$

Similarly, it can be shown that $H(t) > 0$ and $T(t) > 0$ for all $t > 0$, and this completes the proof. □

Invariant region

Since the model monitors changes in the human population, the variables and the parameters must be positive for all $t \geq 0$. The analysis of system (3.2) will therefore be analysed in

a region Ω_1 of biological interest. We have the following lemma on the region that system (3.2) is restricted to.

Lemma 3.2.2. *The feasible region* Ω_1 *defined by*

$$\Omega_1 = \left\{ (S(t), L(t), H(t), T(t)) \in \mathbb{R}^4_+ | S + L + H + T \leq \frac{\pi}{\mu} \right\}$$

is bounded, positively invariant and attracting with respect to system (3.2) for all $t > 0$.

Proof. The total population in this model is clearly not constant. Therefore, the evolution equation of the population is given by

$$\begin{aligned} \frac{dN}{dt} &= \pi - \mu N - \delta_1 H - (k + \delta_2) T, \\ &\leq \pi - \mu N. \end{aligned} \tag{3.3}$$

It can easily be shown that

$$N \leq \frac{\pi}{\mu} + \left(N_0 - \frac{\pi}{\mu} \right) e^{-\mu t} \quad \text{where} \quad N(0) = N_0 \tag{3.4}$$

From (3.4), we observe that as $t \to \infty$, $N(t) \to \frac{\pi}{\mu}$. So if $N_0 \leq \frac{\pi}{\mu}$ then $\lim_{t\to\infty} N(t) = \frac{\pi}{\mu}$. Clearly, $\frac{\pi}{\mu}$ is the upper bound of N. It therefore follows from this result that $(S(t), L(t), H(t), T(t))$ of the model (3.2) satisfies

$$\limsup_{t\to\infty} (S(t), L(t), H(t), T(t)) \leq \frac{\pi}{\mu}.$$

On the other hand, if $N_0 > \frac{\pi}{\mu}$, then N will decrease to $\frac{\pi}{\mu}$ as $t \to \infty$. This means that if $N_0 > \frac{\pi}{\mu}$, then the solution $(S(t), L(t), H(t), T(t))$ enters Ω_1 or approach it asymptotically. Hence Ω_1 is bounded and positively invariant under the flow induced by system (3.2). Therefore, in Ω_1, the model (3.2) is well-posed and it is sufficient to study the dynamics of the model in Ω_1. □

3.3 Threshold Number

The central concept in analysing and quantifying the transmission of the infection is the reproduction ratio R_0. As defined by Macdonald [56], the reproduction number is "*the number of secondary infections produced by a single infective individual in an entirely susceptible population*". We consider our heterogeneous population that can be grouped into

four homogeneous compartments. We let $x = (S, L, H, T)^t = (x_1, x_2, x_3, x_4)^t$ denote the individuals in each compartment and $(\cdot)^t$ denotes a transpose of a matrix. It is known that $x_i \geq 0$ for $i = 1, 2, 3, 4$. The state space of the model is restricted to the closed positive cone $x \in X = \mathbb{R}^4_+$. We sort the compartments in such a way that, the last three compartments are associated with drug use. Then

$$X_s = \{x \geq 0 | x_i = 0, i = 2, 3, 4\}, \tag{3.5}$$

is the set of drug free states. Using these definitions, the model system of differential equations (3.2) given on X_s is given as.

$$\dot{x} = f(x) \tag{3.6}$$

The function (3.6) is comprised of the appearance of new infections (initiations) in a compartment and transfer rates in and out of the compartment. Note that, if ν_i^+ denotes the rate of transfer of individuals into a compartment i, ν_i^- the rate of transfer of individuals out of compartment i, and $\mathcal{F}$, the rate of appearance of new individuals into compartment i, then the components of f are $f_i(x) = \mathcal{F}_i(x) - \nu_i(x)$, where $\nu_i(x) = \nu_i^- - \nu_i^+$. According to our model, each of the functions is at least C^1 in each variable and the following conditions [100] are satisfied.

1. If $x \geq 0$, then f_i, ν_i^+, $\nu_i^- \geq 0$ for i = 1,2,3,4
2. If $x = 0$, then $\nu_i^- = 0$, thus if $x \in X_s$ then $\nu_i^+ = 0$ for i = 2,3,4
3. $\mathcal{F}_i = 0$ for $i = 1$
4. if $x \in X_S$, then $f_i(x) = 0$ and $\nu_i^+(x) = 0$ for $i = 2, 3, 4$

We note that conditions 1. and 2. together with the smoothness assumption on the functions involved guarantee that, the non negative cone $(x_i \geq 0, i = 1, 2, 3, 4)$ is forward invariant and for each non-negative initial condition a unique non-negative solution exists. Condition 3, indicates that the incidence of drug use for non-users is zero and it is satisfied by the system. This indicates that the eigenvalues of the Jacobian at the DFSS all have negative real parts, see Subsection 3.3.1. Condition 4, ensures that the drug free subspace

is invariant and if the population is free of substance abuse, they remain free. This ensures that there is no immigration of drug users who are not density independent.

We assume that the drug free steady state exists and it is locally asymptotically stable. By this assumption, if $\mathbf{E}_0$ denotes the drug free equilibrium of the system, then $\mathcal{F}(x)$ is set to zeros and all the eigenvalues of $Df(x_0)$ have negative real parts.

We obtain the model basic reproduction number using the next generation matrix method described in [100]. The infective classes involved are L, H, T. We decompose the rates of change $(dL/dt, dH/dt, dT/dt)$ of the infective classes in terms of two matrices f_i and ν_i where, f_i represents new infections and ν_i represents transitions. Then we evaluate,

$$F = \left[\frac{\partial f_i}{\partial x_j}(x_0)\right] \quad \text{and} \quad V = \left[\frac{\partial \nu_i}{\partial x_j}(x_0)\right].$$

x_0 is the drug free equilibrium. F is non-negative and V is non-singular. Therefore,

$$f_i = \begin{pmatrix} \Lambda S \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad F = \begin{pmatrix} \beta & \eta_1\beta & \eta_2\beta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

In the same way the transition matrix for the model is given by

$$\nu_i = \begin{pmatrix} -\gamma_2 H + Q_1 L \\ -\sigma L - \gamma_3 T + Q_2 H \\ -\rho H + Q_3 T \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} Q_1 & -\gamma_2 & 0 \\ -\sigma & Q_2 & -\gamma_3 \\ 0 & -\rho & Q_3 \end{pmatrix},$$

where

$$Q_1 = (\mu + \sigma + \gamma_1), \quad Q_2 = (\mu + \gamma_2 + \delta_1 + \rho) \quad \text{and} \quad Q_3 = (\mu + k + \delta_2 + \gamma_3).$$

The basic reproduction number is given as the spectral radius of the next generation matrix

$$R_0 = \rho(FV^{-1}) = R_{01} + R_{02} + R_{03}, \tag{3.7}$$

such that

$$R_{01} = \left(\frac{\beta}{Q_1}\right)\left(\frac{1-\Phi_1}{1-(\Phi_1+\Phi_2)}\right),$$
$$R_{02} = \left(\frac{\beta\eta_1}{Q_2}\right)\left(\frac{\sigma}{Q_1}\right)\left(\frac{1}{1-(\Phi_1+\Phi_2)}\right),$$
$$R_{03} = \left(\frac{\beta\eta_2}{Q_3}\right)\left(\frac{\sigma}{Q_1}\right)\left(\frac{\rho}{Q_2}\right)\left(\frac{1}{1-(\Phi_1+\Phi_2)}\right),$$

where

$$\Phi_1 = \frac{\rho\gamma_3}{Q_2Q_3} \quad \text{and} \quad \Phi_2 = \frac{\gamma_2\sigma}{Q_2Q_1}.$$

Φ_2 is the probability of moving from one of the compartments L and H to the other and back again. Φ_1 is the probability of moving from one of the compartments H and T to the other and directly back. Each time a light user enters a heavy using class, the expected number of new initiations is $\frac{\eta\beta}{Q_2}$, since $\frac{1}{Q_2}$ is the average waiting time of heavy users at that level of infection. The value $\frac{\sigma}{Q_1}$ is the probability that a light user escalates into heavy drug use after first being initiated. The term $\Phi_1 + \Phi_2$ represents the probability that a heavy drug user leaves his class and returns. Using binomial theorem to the first three terms, the term $\frac{1}{1-(\Phi_1+\Phi_2)} \simeq 1 + (\Phi_1 + \Phi_2) + (\Phi_1 + \Phi_2)^2 + ...$, is the expected number of visits to the H class given that an individual has advanced to H. This result is consistent with the multi stage infection model [61] with three infectious classes.

3.3.1 Model Analysis

Drug Free Steady State

The drug free steady state is established when $L^* = 0, H^* = 0, T^* = 0$. From the first equation of (3.2), we obtain $S^* = \frac{\pi}{\mu}$. Therefore, the drug free steady state is given by

$$E_0 = (S^*, L^*, H^*, T^*) = \left(\frac{\pi}{\mu}, 0, 0, 0\right) \tag{3.8}$$

When there is no substance abuse in the population, the susceptible population corresponds to the total population with a constant steady state $N^* = S^* = \frac{\pi}{\mu}$. This steady state is assumed to have a constant inflow from the non core population at a rate π and an outflow

μ, such that an individual is expected to remain in the S compartment an average of μ^{-1} years.

Local Stability of the Drug Free Steady State (DFSS)

To determine the local stability of the DFSS, we evaluate the Jacobian of the system (3.2) at the DFSS. The Jacobian matrix of system (3.2) is given by

$$J(S,L,H,T) = \begin{pmatrix} -\mu-\Lambda & -\frac{\beta S}{N} & -\frac{\beta\eta_1 S}{N} & -\frac{\beta\eta_2 S}{N} \\ \Lambda & \frac{\beta S}{N} - Q_1 & \frac{\beta\eta_1 S}{N} + \gamma_2 & \frac{\beta\eta_2 S}{N} \\ 0 & \sigma & -Q_2 & \gamma_3 \\ 0 & 0 & \rho & -Q_3 \end{pmatrix}.$$

Evaluating the Jacobian at the drug free equilibrium, we obtain

$$J\left(\frac{\pi}{\mu},0,0,0\right) = \begin{pmatrix} -\mu & -\beta & -\beta\eta_1 & -\beta\eta_2 \\ 0 & \beta - Q_1 & \beta\eta_1 + \gamma_2 & \beta\eta_2 \\ 0 & \sigma & -Q_2 & \gamma_3 \\ 0 & 0 & \rho & -Q_3 \end{pmatrix}. \tag{3.9}$$

We consider stability of the drug free steady state by calculating the eigenvalues of the Jacobian (3.9). The characteristic equation for the eigenvalues is given by

$$(\lambda+\mu)[\lambda^3 + A\lambda^2 + B\lambda + C] = 0, \quad \text{where} \tag{3.10}$$

$$\begin{aligned} A &= Q_1 + Q_2 + Q_3 - \beta = Q_2 + Q_3 + \tfrac{Q_1}{1-\Phi_1}\left[R_{01}\Phi_2 + (1-\Phi_1)(1-R_{01})\right] > 0, \\ B &= \tfrac{Q_1Q_3}{(1-\Phi_1)}\left[(1-\Phi_1)(1-R_{01}) + R_{01}\Phi_2\right] + Q_1Q_2\left[(1-\Phi_2)(1-R_{02}) + R_{02}\Phi_2\right] \\ &\quad + \frac{Q_2Q_3}{\sigma\eta_2\rho}\left[(1-\Phi_1)(\sigma\eta_2\rho - R_{03}Q_1Q_2)\right], \\ C &= Q_1Q_2Q_3[1-(\Phi_1+\Phi_2)](1-R_0). \end{aligned}$$

Note that if $\sigma\eta_2\rho \geq R_{03}Q_1Q_2$ when $R_0 < 1$, then the coefficient B will be strictly positive. Otherwise, we can not conclude on the sign of B and it entirely depends on the model parameters.

It can easily be shown that $Q_1Q_2Q_3[1-(\Phi_1+\Phi_2)] > 0$. Note also that, the drug free

steady state exists when $R_0 < 1$ therefore $C > 0$. The characteristic equation immediately gives one eigenvalue $\lambda_1 = -\mu < 0$ and the other eigenvalues are obtained by solving the characteristic equation

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0. \tag{3.11}$$

We analyse the system using Routh-Hurwitz criterion [65], which states that, " if $A > 0, C > 0$ and $AB - C > 0$, then the eigenvalues have negative real parts". Given the nature of the constants A, B and C, we can not easily decide on the sign of the expression $AB - C$. However, using the sum and product of roots of the cubic polynomial equation (3.11), all eigenvalues have negative real parts if and only if $R_0 < 1$. Therefore, the DFSS is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.

This result is further supported by the simulation of the characteristic polynomial, equation (3.11) using parameter values in Table 3.2. The plot of eigenvalues is indicated in Figure 3.2. In the region r_1 ($R_0 < 1$), all eigenvalues have negative parts; in regions r_2, and r_3 ($R_0 > 1$) at least one of the eigenvalues has a positive real.

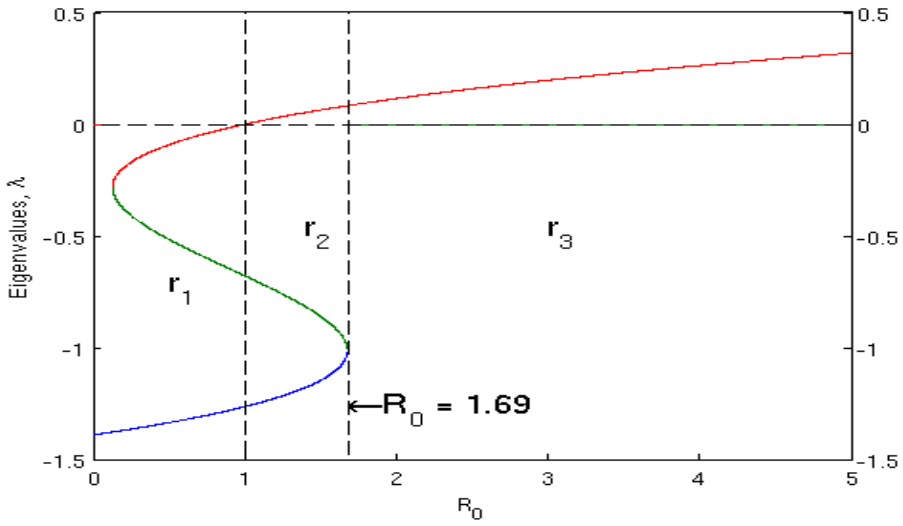


Figure 3.2. Shows the eigenvalues obtained from the characteristic polynomial

We can summarize the results in the following ways;

1. When $R_0 < 1$, the drug free steady state is locally asymptotically stable if $AC - D > 0$. The interpretation of this is that the successively "initiated generation" is smaller than its predecessor, and substance abuse can not persist.

2. When $R_0 > 1$, the drug free steady state is unstable. Thus, drug use persists since the successively "initiated generation" is greater than its predecessors and number of substance users is expected to initially increase. However, this does not go on indefinitely. We relate this trend to infectious disease as observed by Heesterbeek and Roberts [78], that the initiation process reduces the "pool of susceptibles", which reduces the probability of drug users contacting with the susceptible population Beginner within their drug using career.

3.4 Global Stability of the Drug Free Steady State

In this section we prove global stability of the drug-free equilibrium $\mathbf{E}_0$ when $R_0 \leq 1$

Theorem 3.4.1. *The disease free equilibrium* $\mathbf{E}_0$ *of system* (3.2) *is globally asymptotically stable if* $R_0 \leq 1$ *and unstable if* $R_0 > 1$.

Proof. Let

$$V(L, H, T) = aL + bH + cT$$

be a candidate lyapunov function for some non negative values of a, b and c. The time derivative of V is given by

$$\begin{aligned}
\dot{V} &= a\dot{L} + b\dot{H} + c\dot{T}, \\
&= a\left[\beta\left(\frac{L + \eta_1 H + \eta_1 T}{N}\right) S + \gamma_2 H - Q_1 L\right] + b\left(\sigma L + \gamma_3 T - Q_2 H\right) + c\left(\rho H - Q_3 T\right), \\
&\leq a\left[\beta\left(L + \eta_1 H + \eta_2 T\right) + \gamma_2 H - Q_1 L\right] + b\left(\sigma L + \gamma_3 T - Q_2 H\right) + c\left(\rho H - Q_3 T\right), \\
&= \left[a(\beta - Q_1) + b\sigma\right] L + \left(a(\beta\eta_1 + \gamma_2) - bQ_2 + c\rho\right) H + \left(a\eta_2 + b\gamma_3 - cQ_3\right) T.
\end{aligned}$$

We now evaluate the coefficients of the suitable Lyapunov function such that the coefficients of H and T are equal to zero. After algebraic manipulations, we obtain

$$a = Q_2 Q_3[1 - \Phi_1], \qquad b = Q_3(\beta\eta_1 + \gamma_2) + \rho\beta\eta_2, \qquad c = \beta\eta_2 Q_2 + \gamma_3(\beta\eta_1 + \gamma_2).$$

Using these coefficients, the time derivative of the lyapunov function can be expressed as

$$\begin{aligned}
\dot{V} &= Q_2 Q_3(1 - \Phi_1)\dot{L} + Q_3(\beta\eta_1 + \gamma_2) + \rho\beta\eta_2)\dot{H} + (\beta\eta_2 Q_2 + \gamma_3(\beta\eta_1 + \gamma_2))\dot{T}, \\
&\leq \left[Q_2 Q_3(1 - \Phi_1)(\beta - Q_1) + \sigma\left(Q_3(\beta\eta_1 + \gamma_2) + \rho\beta\eta_2\right)\right] L, \\
&= Q_1 Q_2 Q_3[1 - (\Phi_1 + \Phi_2)](R_0 - 1)L.
\end{aligned}$$

For $R_0 \leq 1$, $\dot{V} \leq 0$; the equality holds only when

(a) $R_0 = 1$, and $L = H = T = 0$ or

(b) $L = 0$.

Let us assume that $R_0 > 1$. Using lemma 5 in [59], we observe that the Jacobian matrix based on only the infectious classes evaluated at the non trivial steady state $(0, 0, 0)$ has a determinant given by $Q_1[1-(\Phi_1+\Phi_2)](R_0-1)$. This is positive when $R_0 > 1$ which yields instability in the system. Therefore, by the LaSalle Theorem [82], the trivial equilibrium is globally asymptotically stable in the invariant feasible region

$$\Omega_1 := \left\{ \mathcal{D} \in \mathbb{R}^4_+ | S + L + H + T \leq \frac{\pi}{\mu} \right\}. \tag{3.12}$$

□

3.5 Persistence of the Model

Persistence with a continuous flow ϕ_t defined on some set $\mathbf{E} \subset \Omega_1$ such that the boundary of $\mathbf{E}$ is invariant under the flow ϕ_t, has widespread applications in modelling of dynamical behaviour of ecological and epidemiological entities [58, 91]. Persistence conveys some idea that for interacting populations none of the component populations becomes "extinct" [14, 26]. According to [27], persistence criteria have been analysed using Lyapunov-like functions and analysing the flow on the boundary of $\mathbf{E}$.

Theorem 3.5.1. *The solution to the model system (3.2) is persistent whenever, $R_0 > 1$.*

Before proving Theorem 3.5.1, let us give the definition of persistence of the solution of system (3.2).

Definition 3.5.1. *The system of equations (3.2) is said to be uniformly persistent if there is an $\eta > 0$ (independent of the initial data) such that every solution of the model $(S(t), L(t), H(t), T(t))$ with some initial conditions (S_0, L_0, H_0, T_0) satisfies*

$$\liminf_{t\to\infty} S(t) \geq \eta, \quad \liminf_{t\to\infty} L(t) \geq \eta,$$
$$\liminf_{t\to\infty} H(t) \geq \eta, \quad \liminf_{t\to\infty} T(t) \geq \eta.$$

Proof. To show persistence of the solution (proof of Theorem 3.5.1), we capitalize on the notion of dynamics of a Euclidean space. Let Ω_1 be a locally compact metric space with

metric d and let $\mathbf{E}_1$, the endemic state be any subset of Ω_1 with boundary $\partial\mathbf{E}_1$ and the interior of $\mathbf{E}_1$, $\mathring{\mathbf{E}}_1$. Suppose we have a continuous flow $\phi(t)$ defined on $\mathbf{E}_1$, such that $\partial\mathbf{E}_1$ is invariant under $\phi(t)$. The flow $\phi(t)$ is said to be point dissipative in $\mathbf{E}_1$ if for each $x \in \mathbf{E}_1$, $\omega(x) \neq \emptyset$ and the invariant set

$$\Omega(\phi(t)) = \bigcup\nolimits_{x\in\mathbf{E}_1} \omega(x) \quad \text{has a compact closure.}$$

If we define the $\omega-$limit set of $\mathbf{E}_1$ as

$$\omega(\mathbf{E}_1) = \bigcap_{T\geq 0} Cl\bigcup\nolimits_{t\geq T} \phi(t)\mathbf{E}_1, \tag{3.13}$$

where

$$\phi(t)\mathbf{E}_1 = \bigcap_{x\in\mathbf{E}_1} \{\phi(t)x\} \quad \text{and } Cl \text{ is the closure of the set.} \tag{3.14}$$

Equivalently this implies that, $y \in \omega(x)$ if and only if there is a sequence $t_n \to \infty$ as $n \to \infty$ such that $\phi(t)x \to y$ as $n \to \infty$.

To show persistence of the model population, it is enough to show that for all $x \in \mathring{\mathbf{E}}_1$

$$\liminf_{t\to\infty} d(\phi(t)x, \partial\mathbf{E}_1) > 0. \tag{3.15}$$

To show the boundary of $\mathbf{E}_1$, we suppose that the drug persistent equilibrium is globally stable and use a suitable Lyapunov function;

$$W = \sum_{i=1}^{4} A_i \left(x_i - x_i^* - x_i^* \ln \frac{x_i}{x_i^*} \right), \tag{3.16}$$

where x_i for $i = 1 \ldots 4$, represent S, L, H and T respectively. We also note that

$$\frac{\partial W}{\partial x_i} = A_i \left(1 - \frac{x_i^*}{x_i} \right), \quad \frac{\partial^2 W}{\partial x_i^2} > 0. \tag{3.17}$$

Therefore, $\mathbf{E}_1^* = (x_1^*, x_2^*, x_3^*, x_4^*)$ is the minimum. Suppose that

$$\liminf_{t\to\infty} S(t) \geq \eta_s, \quad \liminf_{t\to\infty} L(t) \geq \eta_l,$$
$$\liminf_{t\to\infty} H(t) \geq \eta_h, \quad \liminf_{t\to\infty} T(t) \geq \eta_t.$$

If we let $\mathbf{E}_1^*$ be the boundary of Ω_1 as $t \to \infty$, then the solutions of $\mathbf{E}_1$ do not escape through the boundaries. Therefore, there exists some $\eta = \min\{\eta_s, \eta_l, \eta_h, \eta_t\}$ such that

$$\liminf_{t\to\infty} x_i(t) \geq \eta \quad \text{for} \quad \text{all} \quad i = 1, 2, 3, 4.$$

This completes the proof □

3.6 Existence and Uniqueness of the Endemic Steady State

The endemic equilibrium $\mathbf{E}_1^* = (S^*, L^*, H^*, T^*)$ of the equation (3.2) satisfies

$$\begin{aligned} 0 &= \pi - \beta\left(\frac{L^* + \eta_1 H^* + \eta_2 T^*}{N^*}\right) S^* - \mu S^* + \gamma_1 L^*, \\ 0 &= \beta\left(\frac{L^* + \eta H^* + \eta_2 T^*}{N^*}\right) S^* + \gamma_2 H^* - Q_1 L^*, \\ 0 &= \sigma L^* + \gamma_3 T^* - Q_2 H^*, \\ 0 &= \rho H^* - Q_3 T^*. \end{aligned} \tag{3.18}$$

An endemic equilibrium $\mathbf{E}_1^* = (S^*, L^*, H^*, T^*)$ satisfies $S^*, L^*, H^*, T^* > 0$. Let A be the matrix of transition states.

$$\mathbf{A} = \begin{pmatrix} -Q_1 & \gamma_2 & 0 \\ \sigma & -Q_2 & \gamma_3 \\ 0 & \rho & -Q_3 \end{pmatrix}. \tag{3.19}$$

The 3×3 matrix $(-\mathbf{A})$ with entries a_{ij} is an M-matrix and satisfies the following properties.

1. $a_{ij} > 0$ for $i = j$
2. $a_{ij} \leq 0$ for $i, j = 1, 2, 3$
3. $(-\mathbf{A})$ is non singular and $(-\mathbf{A})^{-1} > 0$. We note that $(-\mathbf{A})^{-1}$ is positive definite and therefore all the eigenvalues of $(-\mathbf{A})^{-1}$ are positive.
4. There exist $\alpha > 0$, such that $(-\mathbf{A})^{-1}x \geq \alpha x$ for $x \geq 0$, [37].

After some tedious row reduction, the inverse of $(-A)$ can be found and is non negative.

$$(-\mathbf{A})^{-1} = \begin{pmatrix} \frac{Q_2Q_3(1-\Phi_1)}{Q_1Q_2Q_3(1-\Phi_1-\Phi_2)} & \frac{\gamma_2Q_3}{Q_2Q_3Q_1(1-\Phi_1-\Phi_2)} & \frac{\gamma_2\gamma_3}{Q_1Q_2Q_3(1-\Phi_1-\Phi_2)} \\ \frac{\sigma Q_3}{Q_1Q_2Q_3(1-\Phi_1-\Phi_2)} & \frac{Q_1Q_3}{Q_1Q_2Q_3(1-\Phi_1-\Phi_2)} & \frac{Q_1\gamma_3}{Q_1Q_2Q_3(1-\Phi_1-\Phi_2)} \\ \frac{\rho\sigma}{Q_1Q_2Q_3(1-\Phi_1-\Phi_2)} & \frac{\rho Q_1}{Q_1Q_2Q_3(1-\Phi_1-\Phi_2)} & \frac{Q_1Q_2Q_3(1-\Phi_2)}{Q_1Q_2Q_3(1-\Phi_1-\Phi_2)} \end{pmatrix}. \tag{3.20}$$

To show uniqueness of the endemic steady state (Theorem. 3.6.1), we follow closely the formulation for the staged-progression model in [37]. Using property 4. of the M-matrices, it follows that

$$\varphi = -(\beta, \beta\eta_1, \beta\eta_2)\mathbf{A}^{-1}(1,0,0)^t > 0, \tag{3.21}$$

and

$$\phi = -(1,1,1)\mathbf{A}^{-1}(1,0,0)^t > 0, \tag{3.22}$$

where $(\cdot)^t$ denotes matrix transpose.

Theorem 3.6.1. *Suppose that the function f satisfies the conditions $(P1)-(P3)$ in section 3.2.1. If $R_0 \leq 1$, the only steady state in Ω_1 is $\mathbf{E}_0$. If $R_0 > 1$, the endemic steady state $\mathbf{E}_1^*$ exists in the interior of Ω_1 and is unique.*

Proof. It is enough to prove that a unique endemic equilibrium $\mathbf{E}_1$ exist if and only if $R_0 > 1$. We show this by writing the drug using classes in equation (3.18) in the form

$$(L^*, H^*, T^*)^t = -\Lambda^* S^* \mathbf{A}^{-1}(1,0,0)^t. \tag{3.23}$$

From equation (3.23), we observe that L^*, H^* and T^* can be uniquely determined from S^*. Pre-multiplying the row vector $(\beta, \beta\eta_1, \beta\eta_2)$ of the contribution of each drug using class with equation (3.23), we obtain

$$(\beta, \beta\eta_1, \beta\eta_2)(L^*, H^*, T^*)^t = -(\beta, \beta\eta_1, \beta\eta_2)\Lambda^* S^* \mathbf{A}^{-1}(1,0,0)^t. \tag{3.24}$$

We now use the general initiation function $\Lambda^* = f(N^*)\beta(L^* + \eta_1 H^* + \eta_2 T^*)$ and equation (3.21), to obtain

$$\beta(L^* + \eta_1 H^* + \eta_2 T^*) = \varphi S^* f(N^*)\beta(L^* + \eta_1 H^* + \eta_2 T^*). \tag{3.25}$$

Since $\beta(L^* + \eta_1 H^* + \eta_2 T^*) \neq 0$, it is clear that

$$\varphi S^* f(N^*) = 1. \tag{3.26}$$

Similarly , pre-multiplying the row vector (1,1,1) on both sides of (3.23) and applying the initiation function, we obtain

$$(L^* + H^* + T^*) = (1,1,1)(L^*, H^*, T^*)^t = \phi p f(N^*) S^* \beta(L^* + \eta_1 H^* + \eta_2 T^*). \tag{3.27}$$

From the first equation of (3.18)

$$f(N^*)\beta(L^* + \eta_1 H^* + \eta_2 T^*)S^* = \pi - \mu S^*. \tag{3.28}$$

This together with equation (3.27) implies that

$$S^* f(\phi\pi + (1-\phi\mu)S^*) = \frac{1}{\varphi}. \tag{3.29}$$

We now show that, the equation (3.29) has a unique positive solution in the interval $(0, \frac{\pi}{\mu})$ when $R_0 > 1$. We use the function

$$y = g(S^*) = S^* f(\phi\pi + (1-\phi\mu)S^*). \tag{3.30}$$

Clearly $g(0) = 0$ and $g(\frac{\Pi}{\mu}) = \frac{\pi}{\mu} f\left(\frac{\pi}{\mu}\right)$

$$g^{'}(S^*) = f(\phi\pi + (1-\phi\mu)S^*) + (1-\phi\mu)S^* f^{'}(\phi\pi + (1-\phi\mu)S^*), \tag{3.31}$$

$$= f(N^*) + N^* f^{'}(N^*) - \pi\phi f^{'}(N^*), \tag{3.32}$$

$$= f(N^*) + (1-\phi\mu)S^* f^{'} > 0. \tag{3.33}$$

Therefore, $y = g(S^*)$ is monotonically increasing and the graph of $g(S^*)$ has at most one point of intersection with the line $y = \frac{1}{\varphi}$. □

We can explicitly compute the endemic equilibrium by setting the left hand side of the system of equations (3.2) to zero. From the last two equations of the resulting system, we obtain

$$T^* = \frac{\rho}{Q_2} H^* \quad , \tag{3.34}$$

$$L^* = \frac{Q_3}{\sigma}(1-\Phi_1)H^*. \tag{3.35}$$

Adding the first two equations of the system (3.2) equated to zero, we obtain

$$\pi - \mu S^* + \gamma_2 H^* - Q_1 L^* = 0. \tag{3.36}$$

We now substitute equation (3.35) in (3.36), to obtain

$$H^* = \mu\left(\frac{\pi}{\mu} - S^*\right)\frac{\sigma}{Q_1 Q_3}\left[\frac{1}{1-(\Phi_1+\Phi_2)}\right]. \tag{3.37}$$

Substituting (3.34) and (3.35) in the second equation of (3.2) equated to zero, we obtain $H^* = 0$ which corresponds to the drug free equilibrium

$$\left(\frac{\pi}{\mu}, 0, 0, 0\right),$$

and

$$H^* = \frac{\sigma Q_2 S^*(R_0 - 1)}{[Q_2 Q_3(1 - \Phi_1) + \sigma Q_2 + \rho\sigma]}. \tag{3.38}$$

Equating (3.38) and (3.37), and simplifying the resulting expressions, we get the drug-persistent steady state expression,

$$\mathbf{E}_1^* = (S^*, L^*, H^*, T^*),$$

where

$$S^* = \frac{\pi[Q_2 Q_3(1 - \Phi_1) + Q_2\sigma + \rho\sigma]}{Q_1 Q_2 Q_3(R_0 - 1)[1 - (\Phi_1 + \Phi_2)] + \mu[Q_2 Q_3(1 - \Phi_1) + Q_2\sigma + \rho\sigma]}, \tag{3.39}$$

$$H^* = \frac{\sigma Q_2 S^*(R_0 - 1)}{[Q_2 Q_3(1 - \Phi_1) + Q_2\sigma + \rho\sigma]}, \tag{3.40}$$

$$L^* = \frac{Q_2(1 - \Phi_1) S^*(R_0 - 1)}{[Q_2 Q_3(1 - \Phi_1) + Q_2\sigma + \rho\sigma]}, \tag{3.41}$$

$$T^* = \frac{\sigma S^*(R_0 - 1)}{[Q_2 Q_3(1 - \Phi_1) + Q_2\sigma + \rho\sigma]}. \tag{3.42}$$

We thus have the following result;

Theorem 3.6.2. *The system* (3.2) *has a unique drug-persistent steady state when* $R_0 > 1$.

3.7 Local Stability of the Endemic Steady State

We use the center manifold theory described in [16] to check local stability of the endemic steady state. Let us consider the system of equations (3.2) with the bifurcation parameter ϕ such that

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^4 \times \mathbb{R} \to \mathbb{R} \quad \text{and} \quad f \in C^2(\mathbb{R}^4 \times \mathbb{R}). \tag{3.43}$$

Assume that 0 is a non-hyperbolic steady state of system (3.2), then $f(0, \phi) = 0$ for all ϕ. Let the linearisation matrix, $\mathbf{A}$ be such that

$$\mathbf{A} = D_x f(0, 0), \tag{3.44}$$

has a left eigenvector denoted by y and the right eigenvector denoted by v. Then the local dynamics of the model around 0 is totally governed by $\mathbf{a}$ and $\mathbf{b}$ [16, 71], where

$$\mathbf{a} = \sum_{k,i,j=1} y_k v_i v_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \tag{3.45}$$

$$\mathbf{b} = \sum_{k,i,j=1} y_k v_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) \tag{3.46}$$

According to [16], the local dynamics of the model around 0 is determined by the signs of $\mathbf{a}$ and $\mathbf{b}$. We detail the condition on the signs of $\mathbf{a}$ and $\mathbf{b}$ and the bifurcation parameter for convenience of interpretation of the stability.

i. $\mathbf{a} > 0$, $\mathbf{b} > 0$, when $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.

ii. $\mathbf{a} < 0$, $\mathbf{b} < 0$, when $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0, is locally asymptotically stable, and there exists a positive unstable equilibrium.

iii. $\mathbf{a} > 0$, $\mathbf{b} < 0$, when $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable and a positive unstable equilibrium appears.

iv. $\mathbf{a} < 0$, $\mathbf{b} > 0$, when ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly, a negative unstable equilibrium becomes positive and locally asymptotically stable.

Let us now redefine the variables (S, L, H, T) as (x_1, x_2, x_3, x_4). Then the system (3.2) can be rewritten as

$$\frac{dx_1}{dt} = f_1 = \pi - \beta\left(\frac{x_2 + \eta_1 x_3 + \eta_2 x_4}{\sum_{i=1}^{4} x_i}\right) - \mu x_1 + \gamma_1 x_2, \tag{3.47}$$

$$\frac{dx_2}{dt} = f_2 = \beta\left(\frac{x_2 + \eta_1 x_3 + \eta_2 x_4}{\sum_{i=1}^{4} x_i}\right) + \gamma_2 x_3 - Q_1 x_2, \tag{3.48}$$

$$\frac{dx_3}{dt} = f_3 = \sigma x_2 + \gamma_3 x_4 - Q_2 x_3, \tag{3.49}$$

$$\frac{dx_1}{dt} = f_4 = \rho x_3 - Q_3 x_4. \tag{3.50}$$

We evaluate the bifurcation parameter ϕ by equating R_0 to one to obtain

$$\phi = \beta^* = \frac{Q_1 Q_2 Q_3[1 - (\Phi_1 + \Phi_2)]}{Q_2 Q_3(1 - \Phi_1) + \eta_\sigma Q_3 + \eta_2 \rho\sigma}. \tag{3.51}$$

We linearise the system of equations (3.2) at the drug free equilibrium and with the bifurcation parameter ϕ to obtain

$$J = \begin{pmatrix} -\mu & -(\beta^* - \gamma_1) & -\beta^*\eta_1 & -\beta^*\eta_2 \\ 0 & \beta^* - Q_1 & \beta^*\eta_1 + \gamma_2 & \beta^*\eta_2 \\ 0 & \sigma & -Q_2 & \gamma_3 \\ 0 & 0 & \rho & -Q_3 \end{pmatrix}. \tag{3.52}$$

The matrix (3.52) has left eigenvectors $y = (y_1, y_2, y_3, y_4)$, where

$$\begin{aligned} y_1 &= 0, \\ y_2 &= Q_2 Q_3(1 - \Phi_1), \\ y_3 &= (\beta^*\eta_1 + \gamma_2)Q_3 + \beta^*\eta_2\rho, \\ y_4 &= \gamma_3(\beta^*\eta_1 + \gamma_2) + \beta^*\eta_2 Q_2. \end{aligned}$$

The right eigenvector associated with the zero eigenvalue of (3.52) is $v = (v_1, v_2, v_3, v_4)$ where

$$v_1 = Q_1 Q_2 Q_3(1 - \Phi_1 - \Phi_2)\left[\frac{\gamma_1(1 - \Phi_1)}{Q_1(1 - \Phi_1 - \Phi_2)} - R_0^*\right], \quad v_2 = \mu Q_2 Q_3(1 - \Phi_1), \tag{3.53}$$

$$v_3 = \mu\sigma Q_3, \qquad v_4 = \mu\sigma\rho, \tag{3.54}$$

where

$$R_0^* = \frac{\beta^* \left[Q_2Q_3(1-\Phi_1) + \eta_1\sigma Q_3 + \eta_2\sigma\rho\right]}{Q_1Q_2Q_3(1-\Phi_1-\Phi_2)}.$$

We now evaluate the non-zero second order mixed derivatives of with respect to the variables where we obtain

$$\frac{\partial^2 f_1}{\partial x_2 \partial x_3} = \frac{\partial^2 f_1}{\partial x_3 \partial x_2} = \beta\frac{(1+\eta_1)\mu}{\pi}, \qquad \frac{\partial^2 f_1}{\partial x_2 \partial x_4} = \frac{\partial^2 f_1}{\partial x_4 \partial x_2} = \beta\frac{(1+\eta_2)\mu}{\pi}, \tag{3.55}$$

$$\frac{\partial^2 f_1}{\partial x_3 \partial x_4} = \frac{\partial^2 f_1}{\partial x_4 \partial x_3} = \beta\frac{(\eta_1+\eta_2)\mu}{\pi}, \qquad \frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -\beta\frac{(1+\eta_1)\mu}{\pi}, \tag{3.56}$$

$$\frac{\partial^2 f_2}{\partial x_2 \partial x_4} = \frac{\partial^2 f_2}{\partial x_4 \partial x_2} = -\beta\frac{(1+\eta_2)\mu}{\pi}, \qquad \frac{\partial^2 f_2}{\partial x_3 \partial x_4} = \frac{\partial^2 f_2}{\partial x_4 \partial x_3} = -\beta\frac{(\eta_1+\eta_2)\mu}{\pi}. \tag{3.57}$$

The non-zero partial derivatives to used in calculating $\mathbf{b}$ are

$$\frac{\partial^2 f_1}{\partial x_2 \partial \phi} = -1, \qquad \frac{\partial^2 f_2}{\partial x_2 \partial \phi} = 1, \tag{3.58}$$

$$\frac{\partial^2 f_1}{\partial x_3 \partial \phi} = -\eta_1, \qquad \frac{\partial^2 f_2}{\partial x_3 \partial \phi} = \eta_1, \tag{3.59}$$

$$\frac{\partial^2 f_1}{\partial x_4 \partial \phi} = -\eta_2, \qquad \frac{\partial^2 f_2}{\partial x_4 \partial \phi} = \eta_2. \tag{3.60}$$

We now substitute the expressions into (3.45) and (3.46) to obtain

$$\mathbf{a} = -\frac{2\beta^*\mu y_2}{\pi}\left[v_2v_4(1+\eta_2) + v_2v_3(1+\eta_1) + v_3v_4(\eta_1+\eta_2)\right],$$
$$\mathbf{b} = \mu Q_2Q_3(1-\Phi_1)\left[Q_2Q_3(1-\Phi_1) + \eta_1\sigma Q_3 + \eta_2\sigma\rho\right].$$

Clearly, we observe that $\mathbf{a} < 0$ and $\mathbf{b} > 0$. Thus, the drug persistent steady state is locally asymptotically stable close to $R_0 = 1$. We can summarise the results in the following theorem.

Theorem 3.7.1. *The drug persistent steady state is locally asymptotically stable when $R_0 > 1$ but only if R_0 is close to 1.*

3.7.1 Global Stability of the Drug Persistent Steady State

In this section, we now prove the global stability of the drug persistent steady state.

Theorem 3.7.2. *The unique drug-persistent equilibrium $\mathbf{E}_1^*$ is globally asymptotically stable if $R_0 > 1$.*

Proof. We propose a lyapunov function W such that

$$V = \left(S - S^* - S^* \ln \frac{S}{S^*}\right) + \alpha_1 \left(L - L^* - L^* \ln \frac{L}{L^*}\right) + \alpha_2 \left(H - H^* - H^* \ln \frac{H}{H^*}\right) + \alpha_3 \left(T - T^* - T^* \ln \frac{T}{T^*}\right), \tag{3.61}$$

where α_1, α_2 and α_3 are positive constants to be determined. We note that $V(x) \geq 0$ for $x \in Int\, \Omega_1$, the interior of Ω_1 and $V(x) = 0$ if and only if $x = x^*$. Then $V(x)$ is positive definite with respect to drug persistent equilibrium $x = \mathbf{E}_1^*$.

The function is continuous for all $S, L, H, T > 0$. We note that (3.61) satisfies the following;

$$\begin{aligned} &\frac{\partial V}{\partial S} = \left(1 - \frac{S^*}{S}\right), \ \frac{\partial V}{\partial L} = \alpha_1 \left(1 - \frac{L^*}{L}\right), \ \frac{\partial V}{\partial H} = \alpha_2 \left(1 - \frac{H^*}{H}\right), \\ &\frac{\partial V}{\partial T} = \alpha_3 \left(1 - \frac{T^*}{T}\right). \end{aligned} \tag{3.62}$$

Taking the second partial derivative of each of the terms in (3.62), we can say that $\mathbb{E}_1^*$ is the only extremum and global minimum of $\mathbb{R}_+^4$. Note that in [37], the coefficients to the Lyapunov function of a similar model were obtained by a recursive method. In this thesis, we use a slightly different approach. The corresponding time derivative of the lyapunov function is given by

$$\frac{dV}{dt} = \left(1 - \frac{S^*}{S}\right) \dot{S} + \alpha_1 \left(1 - \frac{L^*}{L}\right) \dot{L} + \alpha_2 \left(1 - \frac{H^*}{H}\right) \dot{H} + \alpha_3 \left(1 - \frac{T^*}{T}\right) \dot{T}. \tag{3.63}$$

We note that the system of equations (3.2) at the endemic steady state satisfy.

$$\begin{aligned} \pi &= \mu S^* + \Lambda^* S^* - \gamma_1 L^*, \\ Q_1 L^* &= \Lambda^* S^* + \gamma_2 H^*, \\ Q_3 T^* &= \rho H^*, \\ Q_2 H^* &= \sigma L^* + \gamma_3 T^*. \end{aligned} \tag{3.64}$$

We Set $\mathbb{E}_1^* = (S^*, L^*, H^*, T^*) \in \Omega_1 \subset \mathbb{R}_+^4$. Using (3.2) and (3.64) it can easily be shown

that.

$$\begin{aligned}\left(1-\frac{S^*}{S}\right)\dot{S} &= \left(1-\frac{S^*}{S}\right)\left[\pi-\Lambda^* S^*-\mu S^*+\gamma_1 L^*\right],\\ &= \left(1-\frac{S^*}{S}\right)\left[\mu S^*+\beta(L^*+\eta_1 H^*+\eta_2 T^*)S^*-\gamma_1 L^*\right.\\ &\quad \left.-\beta(L+\eta_1 H+\eta_2 T)S-\mu S+\gamma_1 L\right],\\ &= \mu S^*\left(2-\frac{S}{S^*}-\frac{S^*}{S}\right)-\gamma_1 L^*\left(1-\frac{L}{L^*}\right)\left(1-\frac{S^*}{S}\right)\\ &\quad +\beta S^*\left(1-\frac{S^*}{S}\right)\left[L^*\left(1-\frac{SL}{S^*L^*}\right)+\eta_1 H^*\left(1-\frac{SH}{S^*H^*}\right)\right]\\ &\quad +\beta\eta_2 S^*T^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{ST}{S^*T^*}\right).\end{aligned} \tag{3.65}$$

From equation (3.65), using the arithmetic-geometric means inequality, it is clear that

$$\mu S^*\left(2-\frac{S}{S^*}-\frac{S^*}{S}\right)\leq 0. \tag{3.66}$$

Note that equality holds at the endemic steady state. Similarly, using equations (3.2) and (3.64), the remaining components of (3.63) can be found as

$$\begin{aligned}\alpha_1\left(1-\frac{L^*}{L}\right)\dot{L} &= \alpha_1\beta S^*\left(1-\frac{L^*}{L}\right)\left[L*\left(\frac{SL}{S^*L^*}-\frac{L}{L^*}\right)+\eta_1 H*\left(\frac{SH}{S^*H^*}-\frac{L}{L^*}\right)\right]\\ &\quad +\alpha_1\left(1-\frac{L^*}{L}\right)\left[\beta\eta_2 S^*T*\left(\frac{ST}{S^*T^*}-\frac{L}{L^*}\right)+\gamma_2 H^*\left(\frac{H}{H^*}-\frac{L}{L^*}\right)\right],\end{aligned} \tag{3.67}$$

$$\alpha_2\left(1-\frac{H^*}{H}\right)\dot{H} = \alpha_2\left(1-\frac{H^*}{H}\right)\left[\sigma L^*\left(\frac{L}{L^*}-\frac{H}{H^*}\right)+\gamma_3 T^*\left(\frac{T}{T^*}-\frac{H}{H^*}\right)\right], \tag{3.68}$$

$$\alpha_3\left(1-\frac{T^*}{T}\right)\dot{T} = \alpha_3\left(1-\frac{T^*}{T}\right)\left(\frac{H}{H^*}-\frac{T}{T^*}\right)\rho H^*. \tag{3.69}$$

Using the third and fourth equations of (3.64), we obtain

$$L^* = \frac{(Q_2Q_3-\rho\gamma_3)}{\rho\sigma}T^*. \tag{3.70}$$

We now let $\left(\frac{S}{S^*},\frac{L}{L^*},\frac{H}{H^*},\frac{T}{T^*}\right)=(U,W,X,Y)$. Using this and the substitution of (3.70) into

(3.65) and (3.68), equation (3.63) then becomes

$$\begin{aligned}\frac{dV}{dt} \leq\ & \beta S^* L^* \left[\left(1-\frac{1}{U}\right)(1-UW)+\alpha_1\left(1-\frac{1}{W}\right)(UW-W)\right] \\ & + \beta\eta_1 S^* H^* \left[\left(1-\frac{1}{U}\right)(1-UX)+\alpha_1\left(1-\frac{1}{W}\right)(UX-W)\right] \\ & + \beta\eta_2 S^* T^* \left[\left(1-\frac{1}{U}\right)(1-UY)+\alpha_1\left(1-\frac{1}{W}\right)(UY-W)\right] \\ & + T^* \left[\alpha_1\left(1-\frac{1}{W}\right)(X-W)\frac{Q_3\gamma_2}{\rho}+\alpha_2\left(1-\frac{1}{X}\right)(W-X)\frac{(Q_2Q_3-\rho\gamma_3)}{\rho}\right] \\ & + \left[\alpha_2\gamma_3\left(1-\frac{1}{X}\right)(Y-X)+\alpha_3 Q_3\left(1-\frac{1}{Y}\right)(X-Y)\right]T^* \\ & - \frac{\gamma_1}{\rho\sigma}(Q_2Q_3-\rho\gamma_3)(1-W)\left(1-\frac{1}{U}\right)T^*.\end{aligned} \tag{3.71}$$

In order to eliminate the coefficients of W, X and Y, we choose the coefficients α_1, α_2 and α_3 such that

$$\alpha_1 = 1, \quad \alpha_2 = \frac{Q_3\gamma_2}{(Q_2Q_3-\rho\gamma_3)}, \quad \alpha_3 = \frac{\gamma_2\gamma_3}{(Q_2Q_3-\rho\gamma_3)} \tag{3.72}$$

Substituting the coefficients (3.72) into (3.71) we obtain

$$\begin{aligned}\frac{dV}{dt} \leq\ & \beta S^* L^* f_1(U) + \beta\eta_1 S^* H^* f_2(U,W,X) + \beta\eta_2 S^* T^* f_3(U,W,Y) \\ & + f_4(U,W,X,Y) + f_5(U,W)\end{aligned} \tag{3.73}$$

Such that

$$f_1(U) = \left(2-\frac{1}{U}-U\right), \tag{3.74}$$

$$f_2(U,W,X) = \left(2-\frac{1}{U}-\frac{UX}{W}+X-W\right), \tag{3.75}$$

$$f_3(U,W,Y) = \left(2-\frac{1}{U}-\frac{UY}{W}+Y-W\right), \tag{3.76}$$

$$f_4(U,W,X,Y) = -\left[\frac{Q_3\gamma_2\gamma_3}{(Q_2Q_3-\rho\gamma_3)}\frac{(Y-X)^2}{XY}+\frac{Q_3\gamma_2}{\rho}\frac{(X-W)^2}{XW}\right]T^*, \tag{3.77}$$

$$f_5(U,W) = -\frac{\gamma_1}{\rho\sigma}(Q_2Q_3-\rho\gamma_3)(1-W)\left(1-\frac{1}{U}\right)T^*. \tag{3.78}$$

From function (3.74), using the arithmetic-geometric means inequality, f_1 is less or equal

to zero with equality only when $U = 1$. The functions f_2 and f_3 can be simplified into

$$f_2(U, W, X) = \left(2 - \frac{1}{U} - U\right) - \frac{(X - W)(U - W)}{W}, \tag{3.79}$$

$$f_3(U, W, Y) = \left(2 - \frac{1}{U} - U\right) - \frac{(Y - W)(U - W)}{W}. \tag{3.80}$$

After some algebraic manipulation and using arithmetic-geometric means inequality, we can show that expressions f_2, f_3 and f_5 are less or equal to zero with equality only at the endemic steady state. We also note that from equation (3.66), since $\mu S^* \neq 0$, then $\left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) = 0$ only if $S = S^*$. This corresponds to the susceptible population at the endemic steady state. Similarly, at the endemic steady state

$$\Lambda = \Lambda^*, \quad H = H^*, \quad L = L^*, \quad T = T^* \tag{3.81}$$

Substituting $S = S^*$ and (3.81) into (3.73), we obtain

$$\frac{dV}{dt} \leq 0, \tag{3.82}$$

where the only compact invariant subset of Ω_1 where equality holds ($dV/dt = 0$) is the singleton $\{\mathbf{E}_1^*\}$. By the LaSalle Invariance Principle [15], $\mathbf{E}_1^*$ is globally asymptotically stable in the interior of Ω_1. This completes the proof. □

3.8 Sensitivity Analysis

In this section we carry out sensitivity analysis to find out the contribution of some vital parameters to the dynamics of the model and ascertain unprecedented behaviour of the model if such input parameters are varied. This helps us to allot qualitatively and quantitatively, the variation in the output of the mathematical model to different input variables. Various methods such as differential sensitivity analysis, one-at-a-time sensitivity measures, factorial design, sensitivity index, importance factors, and subjective sensitivity analysis [38], have been used to carry out sensitivity analysis. Of all these methods, subjective sensitivity analysis is the only qualitative method and it relies on the opinion of experienced investigators [38]. In this thesis, we use sensitivity indices by determining the relative change in the reproduction number when a model parameter changes. We use the normalised forward sensitivity index of the reproduction number to the model parameters described in [19, 38]. This is defined as the relative change in the variable R_0 to the relative

change in the parameter. We let R_0 be a differentiable function of each of the parameters.

Definition 3.8.1. *Let R_0 be a differentiable function on the parameter ϱ, then the normalised forward sensitivity index of R_0 at ϱ is defined as*

$$\Upsilon_{\varrho}^{R_0} = \frac{\partial R_0}{\partial \varrho} \times \frac{\varrho}{R_0}. \tag{3.83}$$

The quotient $\frac{\varrho}{R_0}$, is introduced to normalise the coefficient by removing the effect of units. In addition, this calculation is based on the assumption that higher order partial derivatives are negligible and that no correlation exists between input parameters [38]. We now use the explicit formula for R_0 in (3.7) and the definition (3.83), to evaluate the analytical expressions for sensitivity of R_0, to the parameters described in Table. 3.2. For example the sensitivity index of R_0 to the contact rate β is given as

$$\Upsilon_{\beta}^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} = 1. \tag{3.84}$$

Clearly, the normalised forward sensitivity index (NFSI) with respect to β does not depend on any of the parameter values. However, we note that increasing the contact is directly proportional to R_0 and therefore increasing β by 2% increases R_0 by the same percentage. Increase in the contact rate consequently increases prevalence of substance abuse, see Figure 3.6. The indices of relative initiation rates of heavy users and drugs users on treatment have obvious structures respectively as

$$\Upsilon_{\eta_1}^{R_0} = 1 - \frac{Q_2Q_3(1-\Phi_1) + \rho\eta_2\sigma}{Q_2Q_3(1-\Phi_1) + \eta_1\sigma Q_3 + \rho\eta_2\sigma}, \tag{3.85}$$

$$\Upsilon_{\eta_2}^{R_0} = 1 - \frac{Q_2Q_3(1-\Phi_1) + \eta_1\sigma Q_3}{Q_2Q_3(1-\Phi_1) + \eta_1\sigma Q_3 + \rho\eta_2\sigma}. \tag{3.86}$$

The rest of the expressions of normalised forward sensitivity indices are complex. Therefore, we evaluate the indices of all the rest of the parameters at the nominal values and give the corresponding results in Table. 3.2. The sign of the calculated value indicates whether, the parameter increases the reproduction number (positive sign) and consequently the prevalence, or reduces the reproduction number (negative sign) and hence the prevalence.

Based on the nominal parameter values, the sensitivity indexes of parameters β, η_1, η_2, σ and γ_3 are positive. The magnitude of the NFSIs of these parameters indicates that, R_0 is more sensitive to changes in β (NFSI=1). The parameters μ , γ_1, γ_2, ρ, δ_1, δ_2 and

k have negative NFSIs and therefore increasing such parameters reduces R_0. Of all such parameters γ_1 with $|\text{NFSI}| = 0.56$ is the most sensitive .

3.9 Numerical Simulations

3.9.1 Parameter Estimation

Natural mortality rate μ: The average life expectancy of Sub-Saharan Africa is 50 years [1] and the corresponding mortality rate is thus 0.02 per year.

Drug related removal rates δ_1 and δ_2. The time people engage in high risk behaviour under the influence of drugs is not known, and probably varies between populations [41]. Therefore, precise estimation of mortality/removal rates related to substance abuse remains a relatively daunting task. In [13], mortality rates related to drugs among crank-cocaine users and injecting drug users are 0.018 and 0.008 respectively. According to [70], a man who stops smoking at 35 years of age can increase his life expectancy by 5 years. We assume a reduction in life expectancy of 14% due to general substance abuse. With the corresponding $\mu = 0.02yr^{-1}$, the mortality rate of heavy users related to substance abuse δ_1 is $0.0028yr^{-1}$. Noting that treatment improves the quality of life, we assume that treatment reduces mortality rate related to drugs by at-least 50%. Thus, we choose $\delta_2 = 0.0014yr^{-1}$.

Progression rate σ. In [17], the progression rate from light use to heavy use is 0.47. This incorporates progressions from light use to moderate use and then escalation heavy use. On the other hand, the value used was 0.024 [5], and between (0.003, 0.004) in [71] specific to methamphetamine users. In three major cities in South Africa 54% of arrestees who tested positive for cannabis had used the drug in the past 30 days. We may assume that all these arrestees had been heavy cannabis users. We can therefore choose a general progression rate of 0.56 per annum.

Recruitment into rehabilitation ρ. Individuals to be put under rehabilitation must meet the Diagnostic and Statistical Manual of Mental Disorder-Fourth Edition (DSM- IV) criteria for substance abuse or substance dependence. in the survey results from at least 80% specialist substance abuse treatment centres, it was observed that the proportion of patients under

the age of 20 years from January 1997 to December 2001, increased from 5.5% to 24.1% and from 7.0% to 22.0% in Cape Town and Durban respectively. In Gauteng, the proportion increase from 9.9% to 23.4% since the between $1998-2001$ [74]. The observed treatment demand for cannabis users is 17% [77]. There was an observed increase in cannabis use in the first two quarters of 2008 in South Africa, and including alcohol, the observed treatment demand for cannabis accounted for 23.5% of all substance abuse [97]. According to [96] treatment of drug users accounted for 20% of all Medicare hospitalisations. We assume this value corresponds to the treatment demand. In [71], the upper limit of the treatment demand $(0.009, 0.3)$ for methamphetamine users corresponds to 30% treatment rate. In this paper, we choose the average treatment demand of 22.3% with the corresponding treatment rate of 0.223.

Parameter	Nominal value	Range	Source	Sensitivity Index
β	0.105	0.10-0.21	[71]	1
η_1	0.8	0-1	Estimated	+0.39
η_2	0.6	0-1	Estimated	+0.14
π	0.040	0.028-0.080	Estimated	
μ	0.020	0.019-0.021	[1]	-0.14
σ	0.560	0.400-0.700	Estimated	+0.15
γ_1	0.200	0.10-0.6	Estimated	-0.56
γ_2	0.20	0.20-0.50	Estimated	-0.13
γ_3	0.25	0.10-0.30	Estimated	+0.12
ρ	0.223	0.17 -0.30	Estimated	-0.20
δ_1	0.003	0.0015-0.0035	Estimated	-0.01
δ_2	0.002	0.0013 -0.002	Estimated	-0.002
k	0.20	0.15-0.50	Estimated	-0.22

Table 3.2. Parameter values used in simulations and sensitivity analysis

3.9.2 Prevalence and Incidence of Substance Abuse

Prevalence of substance abuse is a mathematical quantity that describes the level of substance abuse in the population. It indicates the proportion of persons in the population who are substance users. This is summarised as

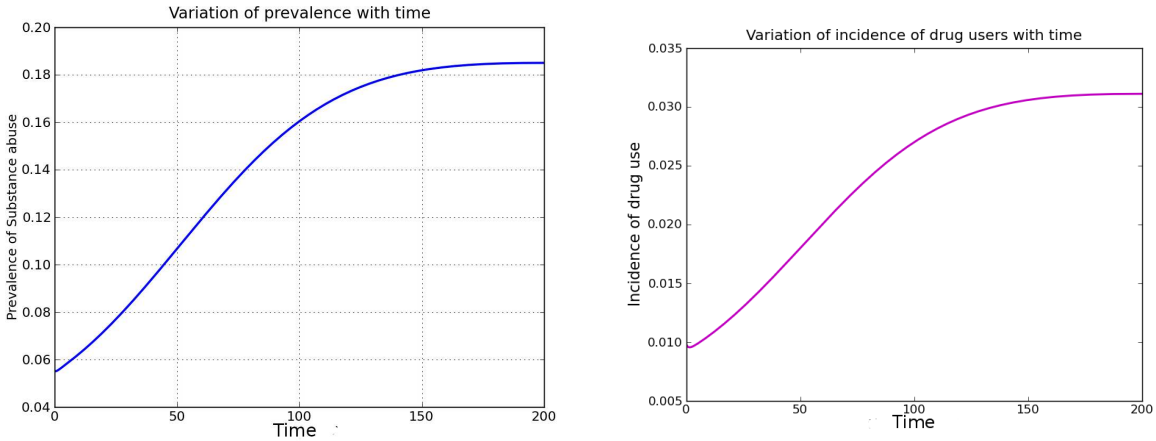
$$Prevalence = \frac{Number\ of\ drug\ users\ in\ the\ population\ at\ a\ given\ time}{Total\ population\ (N)}.$$

Therefore, prevalence of substance abuse is a measure of the burden of substance abuse in the population.

The incidence of substance abuse is given as a mathematical quantity describing the occurrence of new drug users in the population within a given period of time. This can be summarised as

$$Incidence = \frac{Number\ of\ new\ drug\ users\ in\ the\ population\ N\ \ at\ a\ time\ t}{Total\ population\ N}.$$

If we view substance abuse as a disease with low cure rate and as a disease where rehabilitation permits long term survival of drug users, then we can reliably claim that incidence will contribute to growth of prevalence. On the other hand, if control measures are put in place to accelerate quitting and increase the removal of drug users from drug using compartments such that the removal rate exceeds the incidence rate, then prevalence will reduce otherwise, prevalence will continuously grow.



(a) (b)

Figure 3.3. Graphical representation of estimated (a) prevalence, (b) incidence.

These two important epidemiological terms are related by the expression given in [2]

$$\text{prevalence odds} = \text{Incidence} \times \text{Duration},$$

and is frequently taken to hold for stationary populations.

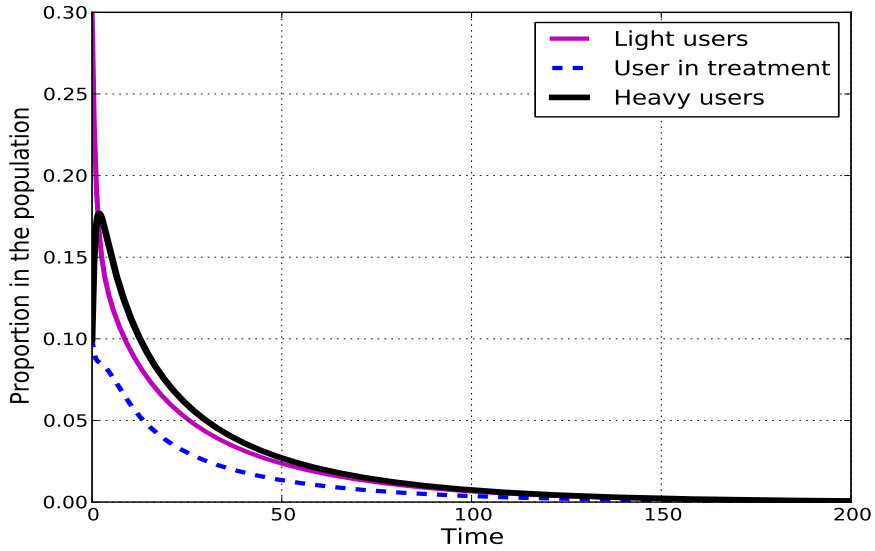


Figure 3.4. Population trajectory when $R_0 = 0.834 < 1$. When $R_0 < 1$, the subsequent generation of drug users is lower than, their predecessors, therefore drug use is consequently eliminated from the population.

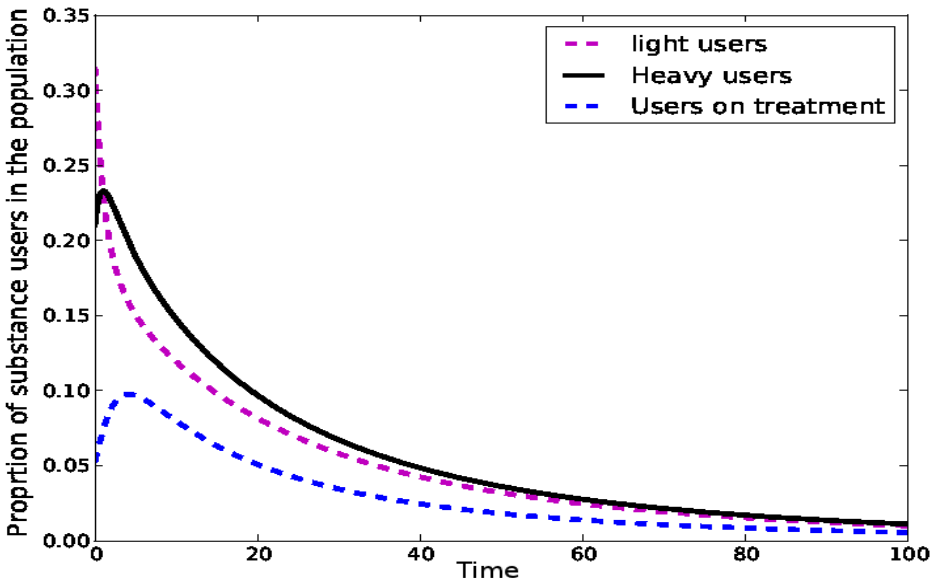


Figure 3.5. Population trajectory when $R_0 = 1.189 > 1$. When R_0 is greater than unity, the subsequent generation of drug users is greater than their predecessors. Therefore, substance abuse persists in the population.

3.9.3 Contribution of amelioration, rehabilitation and relapse

In this subsection, we present numerical results showing the impact of some key parameters in drug epidemics. The contribution of amelioration, rehabilitation and relapse is modelled through the parameters γ_2, ρ and γ_3 respectively.

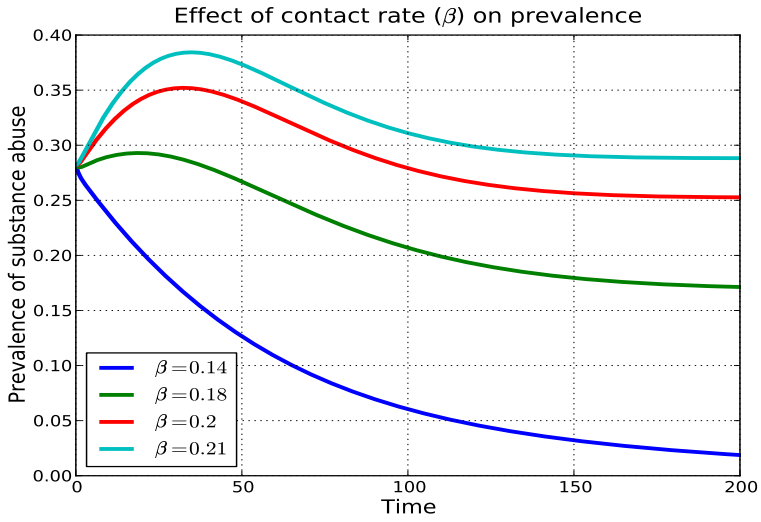
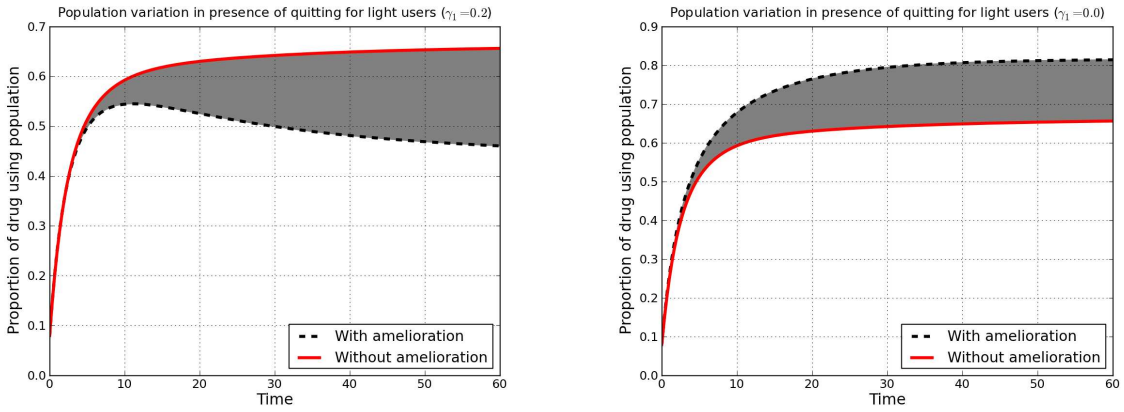


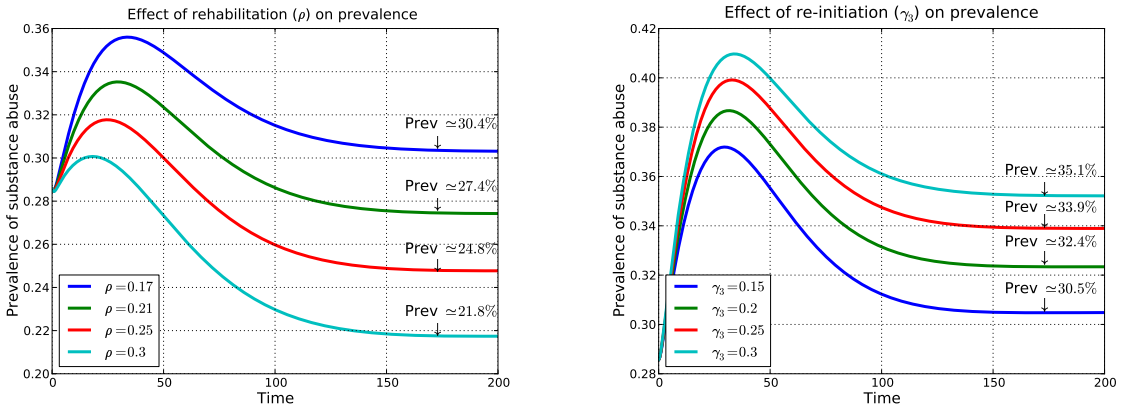
Figure 3.6. Effect of contact rate β on prevalence of substance abuse



(a) (b)

Figure 3.7. Shows the impact of amelioration on prevalence of substance abuse: (a) indicates that, amelioration in presence of quitting for light users ($\gamma_1 = 0.2$) reduces prevalence whereas, (b) amelioration in absence of quitting for light ($\gamma_1 = 0$) increases the prevalence of substance abuse.

To investigate the contribution of contact, we vary the values of contact rate i.e $\beta = \{0.14, 0.18, 0.20, 0.21\}$ and obtain the corresponding plots of prevalence in the population evolving over time, Figure 3.6. The respective values of the reproduction number obtained are, $R_0 = \{0.94, 1.20, 1.34, 1.41\}$. We note from the obtained values that, a unit increase in contact rate β, increases the reproduction number, R_0 by six folds and hence the prevalence of substance abuse. The increase in Prevalence is due to the fact that; if the number of contacts (c) is kept constant, increased contact rate ($\beta = c\hat{\beta}$) increases the probability ($\hat{\beta}$) that a contact will result into an individual being initiated. In Figure 3.7, the shaded part is the contribution of amelioration in increasing or decreasing prevalence. We observe that quitting of light users has implications in drug control strategies as early identification has positive results.



(a) Impact of treatment/rehabilitation on prevalence of substance abuse

(b) Impact of re-initiation/relapse on prevalence of substance abuse

Figure 3.8. Shows the impact of rehabilitation and re-initiation on the prevalence of substance abuse

We observe the changes in prevalence as re-initiation/relapse rate changes. Leaving the other parameters constant, we present some different relapse rates from 15% to 30% and indicate the different scenarios of prevalence curves in Figure 3.8(b). The reproduction number is observed to increase from 1.4387 to 1.5436 (this is consistent with the corresponding positive normalised forward sensitivity index in Table. 3.2) and substance abuse prevalence increases from approximately 30.5% to 35.1%. This indicates that, on average a 15% increase in re-initiation increases the prevalence of substance abuse by approximately 5%. This increase in prevalence with relapse is due to relapse creating cycling of drug

users, who in turn contribute to the initiation process.

Varying the rehabilitation/treatment coverage to a level of 17% to 30% to find out the group of drug users to be targeted and make rehabilitation more effective, the reproduction number is observed to reduce from 1.44 to 1.28 and consequently prevalence reduces from approximately 30.4% to 21.8%, Figure 3.8(a). Therefore, keeping other parameters constant, a unit percentage increase in rehabilitation/treatment of problematic drug users results in approximately 0.66% decrease in prevalence.

3.10 Summary

The model is designed and used to study the dynamics of substance abuse in the population. The heterogeneous population has been classified into homogeneous classes with relatively equal frequency of substance abuse. The model incorporates removal rates related to substance abuse mainly for the drug users at acute/chronic levels of problematic drug use. Sensitivity analysis of the threshold number on the model parameters has been done to identify the vital parameters that influence prevalence of substance abuse. Below are the results of our study on this model with amelioration.

1. The model considered in this study has a globally asymptotically stable drug free steady state whenever $R_0 < 1$. Therefore, substance abuse can be eliminated if control measures are put in place and efforts are directed towards reducing the threshold number to a value less than unity. Otherwise, if $R_0 > 1$, the drug free steady state is unstable and the drug persistent steady state globally stable. Hence, substance abuse remaining endemic in the population.

2. Based on the numerical results and sensitivity analysis, substance abuse can be reduced by; reducing the contact rate β, the relative initiation rates η_1 and η_2, the re-initiation rate γ_3 and the the progression rate σ. These parameters have positive normalised sensitivity indices, as indicated in Table 3.2. The rest of the parameters with negative normalised sensitivity indices have a more dominant inverse proportionality with R_0. Therefore, efforts resulting in increase of such parameters, reduce the prevalence of substance abuse.

3. Amelioration is observed to reduce the prevalence of substance abuse, see Figure 3.7(a). The numerical results with amelioration are consistent with the normalised sensitivity index value in Table 3.2. This is possible because the model incorporates quitting for light users γ_1. On the other had, if there is no quitting for light users in the model, amelioration creates cycling of drug users, thus increasing prevalence, see Figure 3.7(b). A similar observation to that of amelioration without quitting for light users was obtained in [84].

4. Treatment and rehabilitation is aimed at improving the quality of life. The program also results in some drug users quitting which reduces the prevalence of substances abuse. However, due to withdrawal symptoms, partial re- initiation/relapse is observed. The amount of substance required when relapsing is approximately the same as that of a heavy using class. Therefore, relapsing users return directly to heavy drug use.

5. In the model, the vital parameters must depend on factors such as age, behaviour, social economic status, occupation, spatial position or stage of the epidemic. Treatment is applied at the chronic level of substance abuse when rehabilitation is paramount and presumed vital in accelerating quitting hence reducing the prevalence of substance abuse, see Figure 3.8(a).

In our model we did not stratify the population according to age. However, we acknowledge the fact that different age groups have different drug using patterns and individuals start using drugs at ages below 15 years, although drug use is much more incident from ages above 15. Therefore, structuring the population in terms of age would give better conclusions on how to control drug epidemics.

Chapter 4

Influence of Drug Barons on the Prevalence of Substance Abuse.

4.1 Introduction

Substance abuse accounts for most of the criminal offences in townships and cites in South Africa [75]. These offences associated with alcohol and illicit drugs use include; possession and sale of illicit drugs, crime to obtain money to purchase drugs and quench drug addiction, driving under the influence of drugs, child abuse and domestic violence among others. At the heart of the dynamics of illicit drug use patterns is a special class of individuals called drug lords. The drug lords, also commonly known as drug barons or kingpins, are individuals who command a sizeable network of individuals involved in illegal trading of drugs. They play a huge role in shaping drug use patterns over time. The patterns are also influenced by progression of users through different drug use states [17]. We use a compartmental model to ascertain the contribution of drug lords, as well as the impact of law enforcement on drug epidemics.

4.2 The Model with Drug Lords

We extend the model given in Chapter 3, by incorporating a compartment of drug lords D. We assume that the drug lords contribute to the initiation into drug use by acting as drug

supply chains, and making potential drug users aware of the availability of the drugs. In our model, we also assume that drug lords are not drug users basing on the assumption that if they are to use substances, they may end up giving out drugs free of charge as they may be intoxicated. The population of drug lords increases due to the increase in the number of drug users following the law of demand and supply. In the model, we suppose that, in addition to natural mortality, drug lords are also removed as a result of law enforcement or failure to compete in the market. We propose a per capita removal rate function $h(r)$ such that the removal of drug lords occurs at a rate $h(r)D$. In this chapter we shall define the removal rate function as

$$h(r) = \begin{cases} r & \text{for} \quad D > 0 \\ 0 & \text{for} \quad D = 0 \end{cases}$$

Similar to the epidemic model with constant removal rate in [103], $r > 0$ implies that law enforcement is kept in full force until the population of drug lords is remarkably reduced to such a value that substance abuse can be eliminated from the community.

The presence of drugs lords changes the force of initiation from Λ (presented in Chapter 3) to a new value $\bar{\Lambda}$ given by

$$\bar{\Lambda} = \Lambda + \alpha_1 D.$$

Drug lords however, exist as an entity that is not usually part of the community. They act as an environment that influences drug use in the community through supplying drugs to potential users. Their influence in community is felt through organised or brutal syndicates that do not accept non payment of supplies. We therefore do not include them as part of the population N under consideration.

The purpose of this chapter is to determine the dynamics of the substance abuse model analysed in Chapter 3, influenced by drug lords and law enforcement. The model diagram Figure 3.1 is modified to include a compartment D. The flow diagram is represented by Figure 4.2.

In this extended model the epidemiological parameters are all also constant. The description of these parameters other than those indicated in Table. 3.1, is given in the Table. 4.1 below:

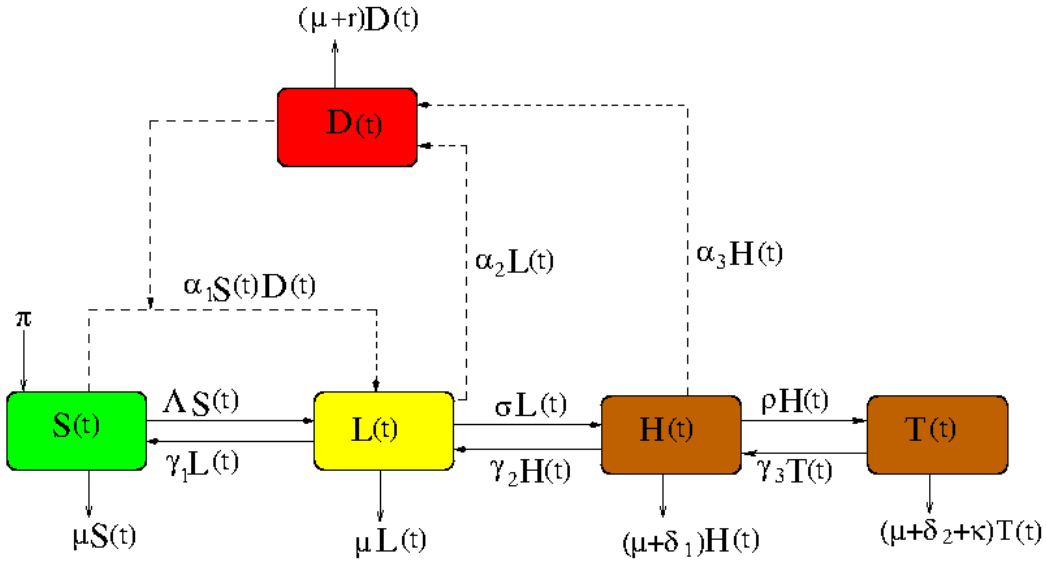


Figure 4.1. Flow diagram shows drugs use dynamics involving drug lords.

Parameter	Description
α_1	The effective contact rate between drug lords and the susceptible population. In this interaction, we view the drug lords as the suppliers of drugs and the drug users as the consumers. It is reasonable to note that, if $D(t) = 0$, also $\alpha_1 = 0$. Therefore, there can be no use of drugs without access to drug although access can result into use [54].
α_2	The fraction of light users whose presence contributes to the escalation of drug lords.
α_3	The fraction of heavy users whose presence contributes to the escalation of drug lords.
r	The removal rate of drug lords which constitutes mainly intervention from law enforcement, community policing, the justice system and incarceration.

Table 4.1. Additional parameters used in the model with drug lords

The ordinary differential equations that represent the compartmental model are

$$\begin{aligned}
\dot{S} &= \pi + \gamma_1 L - \Lambda S - \alpha_1 S D - \mu S, \\
\dot{L} &= \Lambda S + \alpha_1 S D + \gamma_2 H - Q_1 L, \\
\dot{H} &= \sigma L + \gamma_3 T - Q_2 H, \\
\dot{T} &= \rho H - Q_3 T, \\
\dot{D} &= \alpha_2 L + \alpha_3 H - Q_4 D,
\end{aligned} \tag{4.1}$$

where

$$Q_1 = (\mu + \sigma + \gamma_1), Q_2 = (\mu + \rho + \gamma_2 + \delta_1), Q_3 = (\mu + \gamma_3 + \delta_2 + k), \quad Q_4 = (\mu + r).$$

4.3 Model Analysis

In this section, we establish some facts relating to long term behaviour of the solution to the system of equations (4.1). We derive and investigate the stability of the equilibrium states; the Drug Free Equilibrium (DFE) and the Drug Persistent Equilibrium (DPE). In our analysis the phase space of (4.1) is based on the assumption that drug lords are not drug users and are not directly involved dynamics of the total population of drug users and the susceptible population. Since the population under consideration is influenced by the population of drug lords, we denote our phase space in this chapter by Ω_2 instead of Ω_1 used in Chapter 3. The phase space is therefore given by,

$$\Omega_2 = \{S, L, H, T > 0 : S + L + H + T = N\}. \tag{4.2}$$

Lemma 4.3.1. *For Ω_2 defined by (4.2), we let $x(t)$ denote the solution of (4.1) with initial conditions $x(0) \in \Omega_2$, then $x(t) \in \Omega_2$ for all $t > 0$.*

Proof. To see that the solution of the system (4.1) starting from any point in Ω_2 remains in Ω_2, we use the total population of substance users $N = S + L + H + T$. The rate of change of the total population is given by,

$$\dot{N} = \pi - \mu N - \delta_1 H - \delta T \leq \pi - \mu N. \tag{4.3}$$

We now solve the differential inequality using a suitable integrating factor to obtain,

$$N \leq \frac{\pi}{\mu} + \left(N_0 - \frac{\pi}{\mu}\right) \exp(-\mu t) \quad \text{for} \quad t \geq 0.$$

If $N_0 < \frac{\pi}{\mu}$, the solution of the differential equation $N = \pi - \mu N$ is monotone increasing and bounded by $\frac{\pi}{\mu}$ as $t \to +\infty$. Otherwise, the solutions are monotone decreasing and bounded above if $N_0 > \frac{\pi}{\mu}$ as $t \to +\infty$. Therefore, the phase space becomes

$$\Omega_2 = \left\{(S, L, H, T) | S + L + H + T \leq \frac{\pi}{\mu}\right\}. \tag{4.4}$$

Following a similar approach in [92], we consider a case in (4.1) when at-least one of the phase space variables is equal to zero e.g $L = 0$, then $\dot{L} \geq 0$. This means that the solution trajectories of (4.1) do not go through the boundary of Ω_2, forward in time. This condition is valid for all phase space variables. Therefore, the phase space (4.4) is positively-invariant and attracting under the flow induced by the system (4.1). □

4.3.1 The Basic Reproduction Number

We define the basic reproduction number R_{0UD} as the expected number of secondary initiations that result from introducing a single drug user and, or a drug baron in a purely susceptible population. We use this R_{0UD} as a fundamental quantity of our analysis to determine the situation when substance abuse can be wiped out or remain prevalent in the population. We use the next generation matrix approach described in [39, 84, 100] to evaluate the basic reproduction number of the model. Then we have,

$$F = \begin{pmatrix} \beta & \beta\eta_1 & \beta\eta_2 & \alpha_1\frac{\pi}{\mu} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} Q_1 & -\gamma_2 & 0 & 0 \\ -\sigma & Q_2 & -\gamma_3 & 0 \\ 0 & -\rho & Q_3 & 0 \\ -\alpha_2 & -\alpha_3 & 0 & Q_4 \end{pmatrix}.$$

The basic reproduction number is given as the spectral radius of the next generation matrix FV^{-1} so that

$$R_{0UD} = \rho(FV^{-1}) = R_{0U} + R_{0D},$$

with

$$R_{0U} = \frac{\beta\left[Q_2Q_3(1-\Phi_1) + Q_3\eta_1\sigma + \rho\eta_2\sigma\right]}{Q_1Q_2Q_3\left(1-(\Phi_1+\Phi_2)\right)} \quad \text{and} \quad R_{0D} = \frac{\alpha_1\pi\left[\alpha_2Q_2(1-\Phi_1) + \sigma\alpha_3\right]}{\mu Q_1Q_2Q_4\left(1-(\Phi_1+\Phi_2)\right)},$$

where

$$\Phi_1 = \frac{\rho\gamma_3}{Q_2Q_3} \quad \text{and} \quad \Phi_2 = \frac{\sigma\gamma_2}{Q_1Q_2}.$$

The reproduction number R_{0UD} is given in two parts indicating the contribution of two different groups in the drug initiation process. The values R_{0U} and R_{0D} measure the average number of new drug users who may be initiated into drug use if a drug user or drug baron respectively is introduced in a purely susceptible population.

The term R_{0U} (contribution of drug users) is the exact value of R_0 obtained and explained in Chapter 3. To describe the drug lords induced contribution to the reproduction number R_{0D}, we write R_{0D} in the form

$$R_{0D} = R^1_{0D} + R^2_{0D},$$

where

$$R^1_{0D} = \frac{\alpha_1 \pi \alpha_2 (1-\Phi_1)}{\mu Q_1 Q_4 \left(1-(\Phi_1+\Phi_2)\right)} \quad \text{and} \quad R_{0D} = \frac{\sigma \alpha_1 \alpha_3 \pi}{\mu Q_1 Q_2 Q_4 \left(1-(\Phi_1+\Phi_2)\right)}.$$

The terms R^1_{0D} and R^2_{0D} indicate the contribution in the initiation of drug users by drug lords who escalated from the presence of light and heavy drug users respectively.

4.4 Drug Persistent Equilibrium

At the drug persistent equilibrium, the system satisfies

$$0 = \pi + \gamma_1 L^* - \Lambda^* S^* - \alpha_1 S^* D^* - \mu S^*, \tag{4.5}$$

$$0 = \Lambda^* S^* + \alpha_1 S^* D^* + \gamma_2 H^* - Q_1 L^*, \tag{4.6}$$

$$0 = \sigma L^* + \gamma_3 T^* - Q_2 H^*, \tag{4.7}$$

$$0 = \rho H^* - Q_3 T^*, \tag{4.8}$$

$$0 = \alpha_2 L^* + \alpha_3 H^* - Q_4 D^*. \tag{4.9}$$

From equations (4.7) and (4.8) we have

$$H^* = \xi_1 L^*, \quad \text{where} \quad \xi_1 = \frac{\sigma}{Q_2(1-\Phi_1)}, \tag{4.10}$$

$$T^* = \xi_2 L^*, \quad \text{where} \quad \xi_2 = \frac{\rho}{Q_3}\xi_1 \quad \text{and}, \tag{4.11}$$

$$D^* = \xi_3 L^* \quad \text{where} \quad \xi_3 = \frac{\alpha_2 Q_2 (1-\Phi_1) + \alpha_3 \sigma}{Q_2 Q_4 (1-\Phi_1)}. \tag{4.12}$$

Using the substitution of equations (4.10) and (4.11) and expression for the initiation function (3.1), the initiation function at the endemic equilibrium can be given by

$$\Lambda^* = \Psi_1 \frac{L^*}{N^*} \quad \text{where} \quad \Psi_1 = \beta(1+\eta_1\xi_1+\eta_2\xi_2).$$

This can also be given in terms of the component R_{0U} of the reproduction number as

$$\Lambda^* = \Psi_2 R_{0U} \frac{L^*}{N^*} \quad \text{where} \quad \Psi_2 = \frac{Q_1(1-(\Phi_1+\Phi_2))}{(1-\Phi_1)}.$$

From equation (4.6)

$$\Psi_1 \frac{L^* S}{N^*} + \alpha_1 \xi_3 S L^* + \gamma_2 \xi_1 L^* - Q_1 L^* = 0,$$
$$L^* \left[\frac{\Psi_1 S^*}{N^*} + \alpha_1 \xi_3 S^* + \gamma_2 \xi_1 - Q_1 \right] = 0.$$

Either $L^* = 0$ or

$$S^* \left(\frac{\Psi_1}{N^*} + \alpha_1 \xi_3 \right) = \Psi_2, \quad \Psi_2 > 0. \tag{4.13}$$

Note that the initiation function Λ^* is zero ($\Lambda^* = 0$) when

$$L^* = 0 \quad \Rightarrow H^* = T^* = 0, \quad \text{and} \quad S^* = \frac{\pi}{\mu}.$$

Consequently, the population of drug lords will reduce to low negligible values over time. So we have the drug free equilibrium given as

$$DFE = \left(\frac{\pi}{\mu}, 0, 0, 0, 0 \right). \tag{4.14}$$

Using equations (4.5) and (4.6), is can easily be shown that

$$S^* = \frac{\pi}{\mu} + J_1 L^* \quad \text{where} \quad J_1 = \frac{\gamma_1 - \Psi_2}{\mu}. \tag{4.15}$$

The total population can then be given as

$$N^* = S^* + \Psi_3 L^*, \tag{4.16}$$
$$= \frac{\pi}{\mu} + (J_1 + \Psi_3) L^* \quad \text{where} \quad \Psi_3 = \frac{Q_2 Q_3 (1 - \Phi_1) + \sigma Q_3 + \sigma \rho}{Q_2 Q_3 (1 - \Phi_1)}. \tag{4.17}$$

We now substitute for S^* (4.15) and N^* (4.17) in equation (4.13) to obtain

$$a_2 {L^*}^2 + a_1 L^* + a_0 = 0, \tag{4.18}$$

where

$$
\begin{aligned}
a_2 &= \alpha_1\xi_1 J_1(J_1+\Psi_3) = \frac{\alpha_1\xi_1}{\mu}\left[\frac{(\gamma_1-\Psi_2)^2}{\mu}+\Psi_3(\gamma_1-\Psi_2)\right],\\
a_1 &= (\alpha_1\xi_3-\Psi_2)(J_1+\Psi_3)+J_1\left(\Psi_1+\frac{\alpha_1\xi_3\pi}{\mu}\right),\\
&= \frac{(\gamma_1-\Psi_1)}{\mu^2}\left[\mu\Psi_2(R_{0U}-1)+2\pi\alpha_1\xi_3\right]+\gamma_2\gamma_3(R_{0D}-1),\\
a_0 &= \tfrac{\pi}{\mu}\Psi_2\left(R_{0UD}-1\right).
\end{aligned}
$$

Therefore, the solution to (4.18) will be given by

$$
L^*_{\{1,2\}} = \frac{-a_1 \pm \sqrt{a_1^2-4a_2a_0}}{2a_2}. \tag{4.19}
$$

We note that the signs of the coefficients a_2 and a_1 depend on the parameter values. To determine the sign of a_0 for different values of R_{0UD}, we now analyse the term $\frac{(1-\Phi_1-\Phi_2)}{1-\Phi_1}$. Note the term $(1-\Phi_1)$ describes the movement of substance users who do not cycle between the compartments H and T. The expression above can be re-written in the form

$$
\frac{(1-\Phi_1-\Phi_2)}{1-\Phi_1} = 1-\frac{\Phi_2}{1-\Phi_1}
$$

If we suppose

$$
\frac{\Phi_1}{1-\Phi_2}<1, \quad \text{then} \quad \Phi_1+\Phi_2<1.
$$

We now substitute for Φ_1 and Φ_2 to obtain

$$
\rho\gamma_3Q_1+\sigma\gamma_2Q_3 < Q_1Q_2Q_3.
$$

We expand both sides and cancel common terms obtaining

$$
0 < Q_3(\mu^2+\mu\gamma_2+\mu\delta_1+\sigma\delta_1)+(\mu+\delta_1+k)(\mu\rho+\sigma\rho+\mu\sigma)+\mu\sigma\gamma_2.
$$

Therefore, the term $\frac{(1-\Phi_1-\Phi_2)}{1-\Phi_1}$ is positive. Since $(1-\Phi_1)>0$, also $(1-\Phi_1-\Phi_2)>0$.

The sign of a_0 depends on the reproduction number; where a_0 is positive (negative) when R_{0UD} is greater than (less than) unity. If $a_2<0$, then the existence of feasible (positive)

solutions will entirely depend on the signs of a_0 and a_1 as follows.

$$\begin{aligned} &\text{If} \quad a_1 > 0, \quad \text{and} \quad \begin{cases} a_0 > 0 & \text{we have one positive solution} \\ a_0 < 0 & \text{No positive solution} \end{cases} \\ &\text{If} \quad a_1 < 0, \quad \text{and} \quad \begin{cases} a_0 > 0 & \text{we have one positive solution} \\ a_0 < 0 & \text{two positive solution} \end{cases} \end{aligned} \tag{4.20}$$

Our analysis for this case can be summarized into the following theorem;

Theorem 4.4.1. *The drug epidemics model (4.1) has;*

(I) a unique drug persistent equilibrium in Ω_2 when $a_0 > 0$ i.e $R_{0UD} > 1$.

(II) two drug persistent equilibria in Ω_2 if $a_1 > 0$ and $a_0 < 0$ i.e $R_{0UD} < 1$.

(III) a unique drug persistent equilibrium in Ω_2 when $a_0 = 0$ and $a_1 > 0$ or $a_1^2 - 4a_2a_0$.

(IV) no drug persistent equilibrium elsewhere.

On the other hand, if $a_2 < 0$, then the a_1 and a_0 as indicated in (4.20) will reverse signs and the system will not make sense epidemiologically.

It is clear from Theorem 4.4.1 case (I) that the model has a unique drug persistent equilibrium whenever $R_{0UD} > 1$. Furthermore, case (III) suggests the existence of a backward bifurcation. If we set the discriminant to zero i.e

$$a_1^2 - 4a_2a_0 = 0,$$

and the result is solved for the critical value of R_{0UD} denoted by R_{0UD}^c, we have

$$R_{0UD}^c = 1 + \frac{\mu a_1^2}{4a_2\pi\Psi_2}, \tag{4.21}$$

below which no drug persistent equilibrium exist.

4.4.1 Global Stability of the DFE

Theorem 4.4.2. *The model system (4.1) has a globally asymptotically stable DFE whenever $R_{0UD} < R_{0UD}^c < 1$.*

Proof. The condition $R_{0UD} < R^c_{0UD} < 1$, ensures existence of a unique drug free equilibrium. We thus choose a Lyapunov function $V = aL + bH + cT + dD$, where the Lyapunov coefficients are such that $a, b, c, d > 0$. The corresponding derivative of the Lyapunov function is given by

$$\begin{aligned}\dot{V} &= a\dot{L} + b\dot{H} + c\dot{T} + d\dot{D},\\ &= a\Lambda S + (b\sigma - aQ_1 + d\alpha_2)L + (a\gamma_2 - bQ_2 + c\rho + d\alpha_3)H\\ &\quad + (b\gamma_3 - cQ_3)T + (a\alpha_1 S - Q_4 d)D.\end{aligned} \tag{4.22}$$

We linearise the Lyapunov derivative (4.22) at the drug free equilibrium. We note that near the DFE, $S \leq \frac{\pi}{\mu}$ and therefore, $\frac{S}{N} \leq 1$. Using this relation, we obtain

$$\begin{aligned}\dot{V} \leq\ & (a\beta + b\sigma - aQ_1 + d\alpha_2)L + (a\beta\eta_1 + a\gamma_2 - bQ_2 + c\rho + d\alpha_3)H\\ &+ (a\beta\eta_2 + b\gamma_3 - cQ_3)T + \left(a\alpha_1\frac{\pi}{\mu} - Q_4 d\right)D.\end{aligned} \tag{4.23}$$

We choose the coefficients a, b, c, d such that the coefficients of H,T and D are zero. We thus obtain

$$\begin{aligned} a &= \mu Q_2 Q_3 Q_4(1-\Phi_1), & b &= \mu Q_3 Q_4(\beta\eta_1 + \gamma_2) + \rho\mu Q_4\beta\eta_2 + \alpha_1\pi\alpha_3\mu Q_3,\\ c &= \frac{\mu Q_2 Q_3 Q_4(1-\Phi_1)\beta\eta_2 + b\gamma_3}{Q_3}, & d &= \alpha_1\pi\mu Q_2 Q_3(1-\Phi_1).\end{aligned}$$

We now substitute the coefficients in (4.23) to obtain

$$\dot{V} \leq \mu Q_1 Q_2 Q_3 Q_4(1-\Phi_1-\Phi_2)\left[R_{0UD} - 1\right]L.$$

Clearly, $\dot{V} \leq 0$ whenever $R_{0UD} \leq 1$ with equality only when $R_{0UD} = 1$ or $L = 0$. Thus, according to the LaSalle Invariance principle [15], the DFE is globally asymptotically stable. This completes the proof. □

4.4.2 Local Stability of the Drug Persistent Equilibrium

We use the center manifold theory described in [16] to determine the local stability of the endemic steady state. Let us consider the system of equations (4.1) with the bifurcation parameter ϕ such that

$$\frac{dx}{dt} = f(x,\phi), f : \mathbb{R}^5 \times \mathbb{R} \to \mathbb{R} \quad \text{and} \quad f \in C^2(\mathbb{R}^5 \times \mathbb{R}). \tag{4.24}$$

Clearly if 0 is the steady state of system (4.1), then $f(0,\phi)=0$ for all ϕ. Let the linearisation matrix, $\mathbf{A}$

$$\mathbf{A}=D_x f(0,0), \tag{4.25}$$

have a left eigenvector denoted by y and a right eigenvector denoted by v. Then the local dynamics of the model around 0 is totally governed by $\mathbf{a}$ and $\mathbf{b}$ [16, 71], where

$$\mathbf{a}=\sum_{k,i,j=1} y_k v_i v_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \tag{4.26}$$

$$\mathbf{b}=\sum_{k,i,j=1} y_k v_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \tag{4.27}$$

Let us now define the terms (S,L,H,T,D) as (x_1,x_2,x_3,x_4,x_5). Then the system (4.1) can be rewritten as

$$\begin{aligned}
\dot{x}_1 &:= f_1 = \pi+\gamma_1 x_2-\beta\left(\frac{x_2+\eta_1 x_3+\eta_2 x_4}{\sum_{i=1}^4 x_i}\right)x_1-\alpha_1 x_1 x_5-\mu x_1,\\
\dot{x}_2 &:= f_2 = \beta\left(\frac{x_2+\eta_1 x_3+\eta_2 x_4}{\sum_{i=1}^4 x_i}\right)x_1+\gamma_2 x_3+\alpha_1 x_1 x_5-Q_1 x_2,\\
\dot{x}_3 &:= f_3 = \sigma x_2+\gamma_3 x_4-Q_2 x_3,\\
\dot{x}_4 &:= f_4 = \rho x_3-Q_3 x_4,\\
\dot{x}_5 &:= f_5 = \alpha_2 x_2+\alpha_3 x_3-Q_4 x_5.
\end{aligned} \tag{4.28}$$

We evaluate the bifurcation parameter ϕ by equating R_{0UD} to one to obtain

$$\phi=\beta^*=\frac{\mu Q_1 Q_2 Q_3 Q_4[1-(\Phi_1+\Phi_2)]-\alpha_1\pi Q_3(\alpha_2 Q_2(1-\Phi_1)+\sigma\alpha_3)}{\mu[Q_2 Q_3 Q_4(1-\Phi_1)+\eta\sigma Q_3+\eta_2\rho\sigma]}.$$

We linearise the system of equations (4.1) at the drug free equilibrium and with the bifurcation parameter ϕ to obtain

$$J=\begin{pmatrix}
-\mu & \gamma_1-\beta^* & -\beta^*\eta_1 & -\beta^*\eta_2 & -\alpha_1\frac{\pi}{\mu}\\
0 & \beta^*-Q_1 & \beta^*\eta_1+\gamma_2 & \beta^*\eta_2 & \alpha_1\frac{\pi}{\mu}\\
0 & \sigma & -Q_2 & \gamma_3 & 0\\
0 & 0 & \rho & -Q_3 & 0\\
0 & \alpha_2 & \alpha_3 & 0 & -Q_4
\end{pmatrix}. \tag{4.29}$$

The matrix (4.29) has a left eigenvector given by $y = (y_1, y_2, y_3, y_4, y_5)^T$, whose components are

$$\begin{aligned}
y_1 &= 0,\\
y_2 &= \mu Q_2 Q_3 Q_4 (1-\Phi_1),\\
y_3 &= (\beta^* \eta_1 + \gamma_2)\mu^2 Q_3 Q_4^2 + \mu\alpha_1\alpha_3\pi Q_3 Q_4 + \beta^*\eta_2\rho\mu Q_4,\\
y_4 &= \beta^*\eta_2\mu Q_2 Q_4 (1-\Phi_1) + \frac{\gamma_3}{Q_3} y_3,\\
y_5 &= \alpha_1 \pi Q_2 Q_3 (1-\Phi_1).
\end{aligned}$$

The right eigenvector associated with the zero eigenvalue of (4.29) is $v = (v_1, v_2, v_3, v_4, v_5)^T$, where

$$\begin{aligned}
v_1 &= Q_1 Q_2 Q_3 Q_4 (1-\Phi_1-\Phi_2)[R^*_{0UD} - R_c] \quad \text{with} \quad R_c = \frac{\gamma_1(1-\Phi_1)}{Q_1(1-\Phi_1-\Phi_2)},\\
v_2 &= \mu Q_2 Q_3 Q_4 (1-\Phi_1), \qquad v_3 = Q_3 Q_4 \sigma\mu,\\
v_4 &= \sigma\mu\rho Q_4, \qquad v_5 = \alpha_2\mu Q_2 Q_3 (1-\Phi_1) + \alpha_3 \mu Q_3 \sigma,
\end{aligned}$$

where

$$\begin{aligned}
R^*_{0UD} &= \frac{\beta^*\left[Q_2 Q_3 (1-\Phi_1) + Q_3\eta_1\sigma + \rho\eta_2\sigma\right)}{Q_1 Q_2 Q_3\left(1-(\Phi_1+\Phi_2)\right]} + \frac{\alpha_1\pi\left[\alpha_2 Q_2(1-\Phi_1) + \sigma\alpha_3\right]}{\mu Q_1 Q_2 Q_4\left(1-(\Phi_1+\Phi_2)\right)},\\
&\text{and} \quad R_c < R^*_{0UD}.
\end{aligned}$$

We now evaluate the non-zero second order mixed derivatives of with respect to the variables. We thus have the following

$$\begin{aligned}
&\frac{\partial^2 f_1}{\partial x_2 \partial x_3} = \frac{\partial^2 f_1}{\partial x_3 \partial x_2} = \beta^* \frac{(1+\eta_1)\mu}{\pi}, && \frac{\partial^2 f_1}{\partial x_2 \partial x_4} = \frac{\partial^2 f_1}{\partial x_4 \partial x_2} = \beta^* \frac{(1+\eta_2)\mu}{\pi},\\
&\frac{\partial^2 f_1}{\partial x_3 \partial x_4} = \frac{\partial^2 f_1}{\partial x_4 \partial x_3} = \beta^* \frac{(\eta_1+\eta_2)\mu}{\pi}, && \frac{\partial^2 f_1}{\partial x_1 \partial x_5} = \frac{\partial^2 f_1}{\partial x_5 \partial x_1} = -\alpha_1,\\
&\frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -\beta^* \frac{(1+\eta_1)\mu}{\pi}, && \frac{\partial^2 f_2}{\partial x_2 \partial x_4} = \frac{\partial^2 f_2}{\partial x_4 \partial x_2} = -\beta^* \frac{(1+\eta_2)\mu}{\pi},\\
&\frac{\partial^2 f_2}{\partial x_3 \partial x_4} = \frac{\partial^2 f_2}{\partial x_4 \partial x_3} = -\beta^* \frac{(\eta_1+\eta_2)\mu}{\pi}, && \frac{\partial^2 f_2}{\partial x_1 \partial x_5} = \frac{\partial^2 f_2}{\partial x_5 \partial x_1} = \alpha_1.
\end{aligned}$$

The non-zero partial derivatives used in calculating $\mathbf{b}$ are

$$\frac{\partial^2 f_1}{\partial x_2 \partial \phi} = -1, \qquad \frac{\partial^2 f_2}{\partial x_2 \partial \phi} = 1,$$
$$\frac{\partial^2 f_1}{\partial x_3 \partial \phi} = -\eta_1, \qquad \frac{\partial^2 f_2}{\partial x_3 \partial \phi} = \eta_1,$$
$$\frac{\partial^2 f_1}{\partial x_4 \partial \phi} = -\eta_2, \qquad \frac{\partial^2 f_2}{\partial x_4 \partial \phi} = \eta_2.$$

We now substitute the expressions into (4.26) and (4.27) to obtain

$$\mathbf{a} = -2\mu Q_2 Q_3 Q_4 (1-\Phi_1) \left[\frac{\mu \beta^*}{\pi} \left(v_2 v_3 (1+\eta_1) + v_2 v_4 (1+\eta_2) + v_3 v_4 (\eta_1 + \eta_2) \right) + v_1 v_5 \alpha_1 \right],$$
$$\mathbf{b} = \mu Q_2 Q_3 Q_4 (1-\Phi_1) \left[\mu Q_2 Q_3 Q_4 (1-\Phi_1) + \eta_1 \mu \sigma Q_3 + \eta_2 \mu \sigma Q_2 \right].$$

We observe that $\mathbf{a} < 0$ and $\mathbf{b} > 0$. We thus have the following result.

Theorem 4.4.3. *The drug persistent steady state is locally asymptotically stable when* $R_{0UD} > 1$ *and* R_{0UD} *close to 1.*

4.5 Numerical Results

In this section, we illustrate the theoretical results of the model by numerically integrating the model system (4.1). The demographic parameters μ, δ_1 and δ_2 which regulate the dynamics of the population of the susceptible population, light users and heavy users respectively, are specific to sub-Saharan Africa. The nominal values of the parameter values used in the model are indicated in Table. 4.5.

The simulations in this chapter are synonymous with those in Chapter 3. In this chapter we concentrate on the influence of drug lords.

We vary the initial population of light drug users and simulate the prevalence of drug user. In the long term Figure 4.2, the prevalence in the evolving population converges to a similar point. To investigate the relationship between law enforcement and contact between drug lords and potential initiates, we vary the contact rate α_1 between drug lords and drug users from 0.04 to 0.3 and present results in Figure 4.5. The prevalence rate is observed to increase from undetectable levels (approximately 0%) to 12.7 (Figure 4.4(a)).

Parameter	nominal value	Range	Source
π	0.04	0.028-0.080	[71]
η_1	0.8	(0-1)	Estimated
η_2	0.6	(0,1)	Estimated
β	0.105	[0.10-0.21]	[71]
σ	0.56	0.40-0.70	Estimated
ρ	0.223	0.17-0.30	Estimated
k	0.20	0.15-0.50	Estimated
μ	0.02	0.019-0.021	[1]
γ_1	0.20	0.10-0.60	Estimated
γ_2	0.4	0.2-0.5	Estimated
γ_3	0.25	0.2-0.5	Estimated
α_1	0.4	0-1	Estimated
α_2	0.04	0-1	Estimated
α_3	0.08	0-1	Estimated
r	0.05	0-1	Estimated

Table 4.2. Parameter values used in the extended model with drug lords

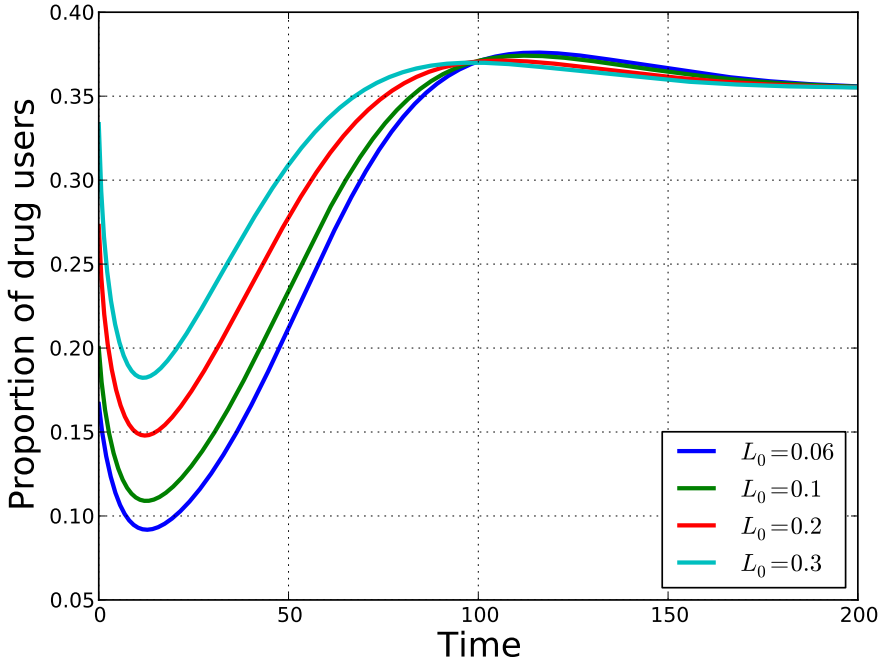


Figure 4.2. Prevalence of substance abuse with different initial population of light drug users

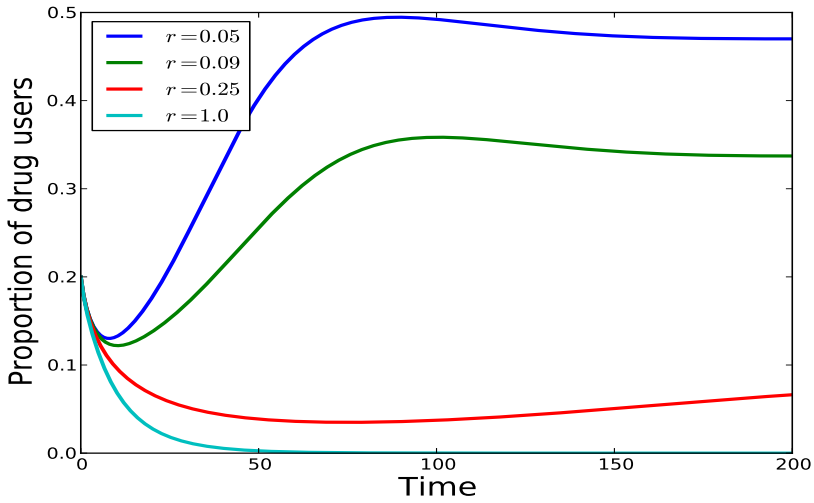
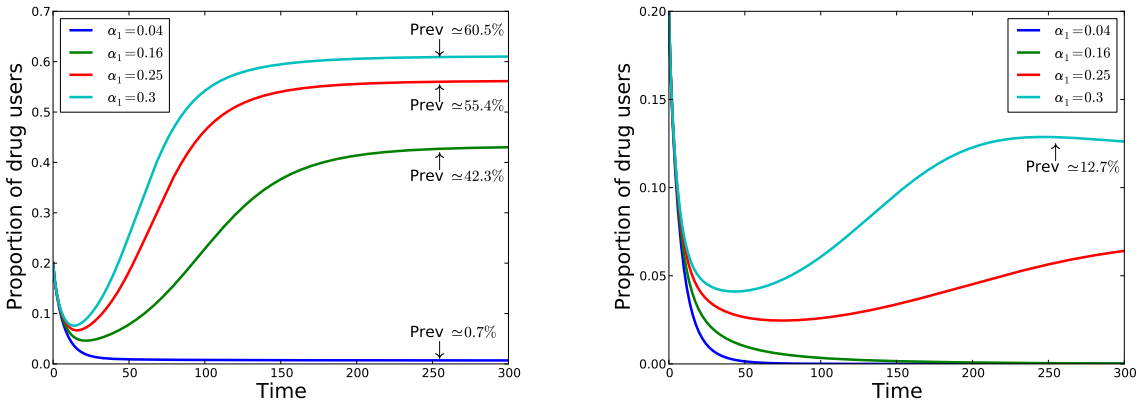


Figure 4.3. The impact of law enforcement on the prevalence of substance abuse



(a) Prevalence of substance abuse without law enforcement, ($r = 0$).

(b) Prevalence of substance abuse with law enforcement ($r = 0.08$).

Figure 4.4. Shows that, given the same initiation potential by drug lords, effective policing and law enforcement, will always keep the prevalence of drug abuse lower than it would have been without law enforcement.

When compared with the case in absence of law enforcement but for similar contact rates between drug lords and drug users, the prevalence of substance abuse is observed to increase from 0.5% to 60.0% (Figure 4.4(b)). In the same way, we observe from Figures. 4.3 and 4.5 that, law enforcement reduces prevalence, and from Figure 4.5 in particular, increasing law enforcement by 8% can reduce prevalence by up to 50%. The reason for such a decrease is due to the fact that; when the population of drug lords reduces, so does the supply of

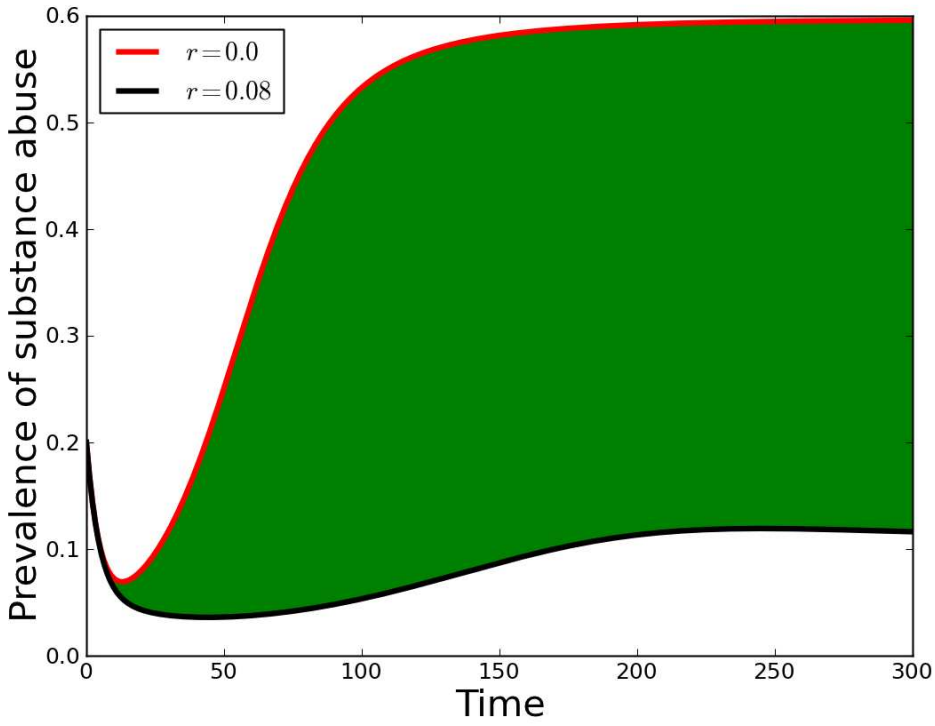


Figure 4.5. Contribution of law enforcement in drug epidemics. The green shading indicates the prevalence can be reduced by up to 50% when law enforcement is increased by approximately 8%. For the interpretation of this figure with regard to colour, the reader is referred to the electronic version.

substances to potential users and the probability that a susceptible individual will meet a drug lord or acquire an addictive substance consequently reduces.

4.6 Summary

In this chapter, we presented a compartmental model for general substance abuse showing the influence of drug lords on the prevalence of substance abuse. Qualitative evaluation of the effectiveness of law enforcement as a means of intervention on general substance abuse epidemic was evaluated. The quantity of law enforcement directed towards curbing problematic drug usage, is not easy to measure. However, we arbitrarily quantified it using numerical values. The resulting plots produced on law enforcement are out of the motivation based on scenario analysis. In this process, we analysed the possible outcomes (trend of drug use prevalence) by considering alternative input values of law enforcement.

The results indicate that stepping up law enforcement reduces the prevalence of substance abuse. The interpretation of this being that; in the ideal case, if drugs were completely unavailable, there would be no drug addiction, see also [36]. Reducing the number of drug lords reduces the probability of a susceptible individual being initiated into substance abuse by a drug lord.

Chapter 5

Impact of Substance Abuse on the Prevalence of HIV

5.1 Introduction

Most abused substances are not only psychoactive and influencing mind swing of the users, they also put the drug users at a risk of contracting infections such as Hepatitis B, Hepatitis C, HIV and other sexually transmitted infections. Heavy drug usage and alcohol heightens sexual urge in men, increasing the probability of the user socializing in areas (such Shebeens) where they can easily find a sexual partner, as well as having multiple partners. In the event of sexual contact, drug users are highly likely not to use condoms, or if they happen to use one, the probability of improper usage is high. In the case of injectable drug use, there is direct administration of potentially contaminated body fluids from one individual to another through needle sharing. In the longitudinal assessment of the effect of drug and alcohol abuse on HIV-1 treatment [55], it was noted that, switching from non use to substance use for HIV infected individuals is associated with worsening antiretroviral therapy (ART) use and adherence, less frequent HIV-1 RNA suppressors and blunted CD4 increases, compared to remaining free from substance use. Alternatively, switching from alcohol and drug use to non use, is associated with general improved health. In HIV seropositive individuals, the immune suppression and immunomodulation further compromise their immune system increasing susceptibility to opportunistic infections and consequently faster progression to AIDS. Therefore, abuse of alcohol and drugs is corre-

lated with the risk of acquiring HIV and consequently, the increase in viral load in the community. In the same way, suppression of the immune system is associated with low CD4 count hence leading to early start of ART for infected individuals.

A number of studies on mathematical modelling involving co-infection dynamics have been done. For example HIV and tuberculosis [4, 79, 85], HIV and Malaria [63] among others. Some studies have also been done with respect to co-dynamics between substance abuse and other infection but little work has been done regarding mathematical modelling. We cite some of the work known to us so far; for example Crack-Cocaine and HIV [13], alcohol and gonorrhea [66], heavy alcohol drinking and HIV [31]. In this chapter, we construct a useful mathematical model for the dynamics of substance abuse and HIV with the interest of finding out the effect of sexual habits (increased sexual activity resulting from high substance consumption) and information dissemination on the prevalence of HIV.

5.2 The Model

To model the impact of substance abuse on the dynamics of HIV, we extend the conceptual compartmental model presented in Chapter 3. In this model, we divide the general population involved in the drug use cycle into two main groups (i.e HIV negative individuals and HIV positive individuals) each with four states (susceptible, light users, heavy users and users under rehabilitation). The total population N_1 evolving over time as divided into non-intersecting subgroups depending on theirs substance abuse and HIV status and is given by

$$N_1(t) = S_1(t) + S_2(t) + L_1(t) + L_2(t) + H_1(t) + H_2(t) + T_1(t) + T_2(t)$$

The notation of the eight compartments is indicated in the Table 5.1. This model is based on the assumption that; (i) there is homogeneous mixing between individuals, (ii) all individuals (S_1, L_1, H_1 and T_1) are susceptible to HIV and all non drug users (S_1 and S_2) are susceptible to initiation into drug use. The susceptible population is generated by a constant recruitment of individuals into the population. Susceptible individuals S_1 can be initiated into substance abuse following effective interaction with substance users as indicated in Chapter 3. In this chapter however, we account for additional initiations

$\beta L_2 S_1/N_1$, $\beta\eta_1\phi_1 H_2 S_1/N_1$ and $\beta\eta_2\phi_2 T_2 S_1/N_1$ due to interaction with HIV-infected drug users L_2, H_2 and T_2 respectively. The initiation function for substance abuse is therefore given by

$$\Gamma = \beta\left(L_1 + L_2 + \eta_1(H_1 + \phi_1 H_2) + \eta_2(T_1 + \phi_2 T_2)\right)/N_1 \tag{5.1}$$

The parameters η_1 and η_2 measure the relative initiation rates of substance users in classes H_1, H_2, T_1 and T_2 compared to L_1 and L_2. We assume that parameters η_1 and η_2 take up value $0 < \eta_1, \eta_2 < 1$ as indicated in Chapter 3. The parameters ϕ_1 and ϕ_2 with $0 < \phi_1, \phi_2 < 1$ account for further reduction in initiation ability by individuals in H_2 and T_2 classes as a result substance abuse symptomatic manifestations and rehabilitation respectively. We note that in absence of HIV infection in the population of drug users, the initiation function (5.1) reduces to the function (3.1) used in Chapter 3.

In the model, we use the non-linear transmission function $f(P) = de^{(-\lambda P)}$ similar to the transmission function used in the Tuberculosis/ HIV co-infection model [4]. The product of the reduced transmission rate of HIV ($f(P) = de^{-\lambda P}$) and the prevalence P give the effective transmission rate for HIV ($g = f(P)P = de^{(-\lambda P)}P$), where parameter d depends on the sexual habits of drug users and the local cofactors for the transmission of HIV such as other sexually transmitted infections, and λ the "the speed at which information on HIV diffuses". It has been clearly noted in [13] that increased awareness of the HIV pandemic influences changes in behaviour for example, injecting cocaine users resorting to cocaine smoking consequently reducing the HIV incidence rate. Although the whole population is susceptible to HIV, we limit our model discussion to the population susceptible to using drugs. HIV-negative individuals (in compartments S_1, L_1, H_1, T_1) can contract HIV through effective contact with HIV-positive individuals (S_2, L_2, H_2, T_2) at an effective transmission rate g. We use this effective transmission rate for both drug users and non-drug users for mathematical tractability. However, we acknowledge the fact that the two groups may not entirely be at the same risk of becoming HIV-positive. Natural mortality rates occur in all compartments at a rate μ_1 for HIV-negative population and μ_2 for the HIV positive population. Similar to H_1 and T_1, individuals in the classes H_2 and T_2 suffer additional removal related to drug use, incarceration and aggravated mortality at constant rates δ_2 and d_2 respectively. The description of parameters of the extended model is given it Table 5.2.

Parameter	Description
S_1	Number of HIV− people not using drugs
S_2	Number of HIV+ people not using drugs
L_1	Number of HIV− light drug users
L_2	Number of HIV+ light drug users
H_1	Number of HIV− heavy drug users
H_2	Number of HIV+ heavy drug users
T_1	Number of HIV− drug users on treatment
T_2	Number of HIV+ drug users on treatment for drugs
N_1	Total population $N_1 = S_1 + S_2 + L_1 + L_2 + H_1 + H_2 + T_1 + T_2$
P	Prevalence of HIV $P = (S_2 + L_2 + H_2 + T_2)/N_1$
g	Effective transmission rate of HIV $g = f(P)P$

Table 5.1. The eight compartments of the model

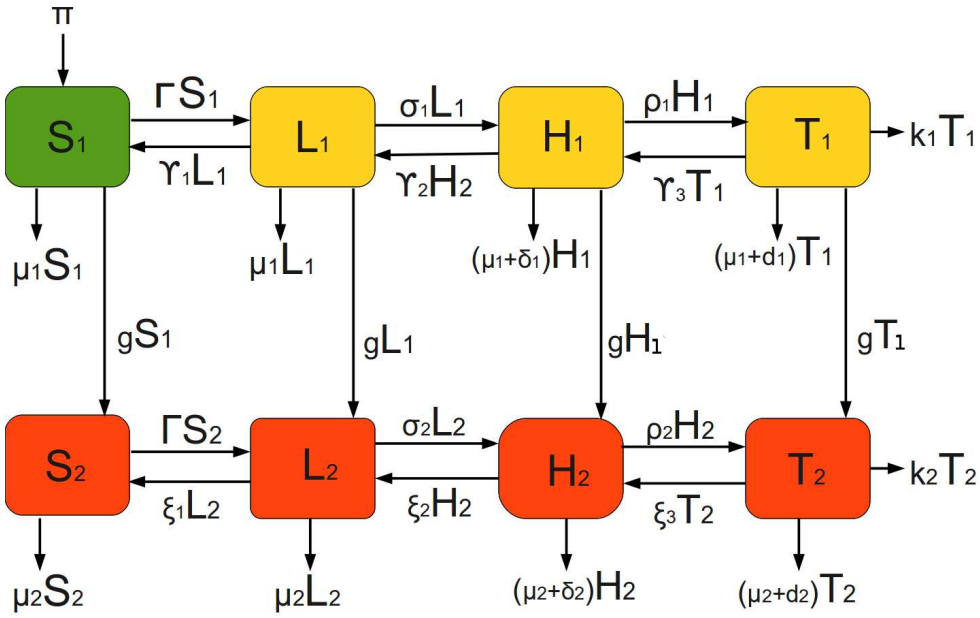


Figure 5.1. Shows the coexistence of substance abuse and HIV

The model equations are given as follows

$$\frac{dS_1}{dt} = \pi + \gamma_1 L_1 - \Gamma S_1 - \mu_1 S_1 - f(P)PS_1, \tag{5.2}$$

$$\frac{dL_1}{dt} = \Gamma S_1 + \gamma_2 H_1 - (\mu_1 + \sigma_1 + \gamma_1)L_1 - f(P)PL_1, \tag{5.3}$$

$$\frac{dH_1}{dt} = \sigma_1 L_1 + \gamma_3 T_1 - (\mu_1 + \delta_1 + \gamma_2 + \rho_1)H_1 - f(P)PH_1, \tag{5.4}$$

$$\frac{dT_1}{dt} = \rho_1 H_1 - (\mu_1 + d_1 + \gamma_3 + k_1)T_1 - f(P)PT_1. \tag{5.5}$$

for $HIV-$ people, and

$$\frac{dS_2}{dt} = f(P)PS_1 + \xi_1 L_2 - \Gamma S_2 - \mu_2 S_2, \tag{5.6}$$
$$\frac{dL_2}{dt} = \Gamma S_2 + f(P)PL_1 + \xi_2 H_2 - (\mu_2 + \xi_1 + \sigma_2)L_2, \tag{5.7}$$
$$\frac{dH_2}{dt} = f(P)PH_1 + \sigma_2 L_2 + \xi_3 T_2 - (\mu_2 + \delta_2 + \xi_2 + \rho_2)H_2, \tag{5.8}$$
$$\frac{dT_2}{dt} = f(P)PT_1 + \rho_2 H_2 - (\mu_2 + d_2 + \xi_2 + k_2)T_2, \tag{5.9}$$

for $HIV+$ people with initial conditions

$$S_1(0) = S_{10} > 0, L_1(0) = L_{10} > 0, H_1(0) = H_{10} > 0, T_1(0) = T_{10} > 0,$$
$$S_2(0) = S_{20} > 0, L_2(0) = L_{20} > 0, H_2(0) = H_{20} > 0, T_2(0) = T_{20} > 0. \tag{5.10}$$

Table 5.2. Description of parameters used in the model.

Symbol	Description
β	The effective contact rate between drugs users and the susceptible population
η_1	The relative ability to initiate new drug users by heavy users
η_2	The relative ability to initiate new drug users by users in rehabilitation
ϕ_1, ϕ_2	Further reduction in Initiation ability by H_2 and T_2 respectively
π	Recruitment rate into the susceptible population
μ_1, μ_2	Natural mortality rate of the HIV_- and HIV_+ population respectively
σ_1, σ_2	The mean rate at which light users escalate to heavy drug use
γ_1, ξ_1	The mean rate at which light users quit and become susceptible again
γ_2, ξ_2	The mean rate at which heavy drug users move back into light drug use
ρ_1, ρ_2	The mean rate at which heavy drug users are recruited into rehabilitation
γ_3, ξ_3	The mean rate at which those under rehabilitation relapse into heavy drug use
δ_1, δ_2	Removal rate related to drug use for heavy drug users
d_1, d_2	Removal rate related to drug use for users under rehabilitation
k_1, k_2	The mean rate at which users in rehabilitation permanently quit

5.3 Positivity of Solutions

The system (5.2)-(5.9) can be analysed in the domain $\Omega_3 \subset \mathbb{R}^8_+$.

Theorem 5.3.1. *The solutions of the system of equations (5.2)-(5.9) with initial conditions (5.10) satisfy* $S_1(t) > 0$, $L_1(t) > 0$, $H_1(t) > 0$, $T_1(t) > 0$, $S_2(t) > 0$,$L_2(t) > 0$, $H_2(t) > 0$,

$T_2(t) > 0$ for all $t > 0$. The region $\Omega_3 \subset \mathbb{R}^8_+$ is attracting with respect to (5.2)-(5.9) and positively invariant.

Proof. Consider the equation

$$\frac{dS_1}{dt} = \pi + \gamma_1 L_1 - \Gamma S_1 - \mu_1 S_1 - f(P)PS_1.$$

clearly

$$\frac{dS_1}{dt} \geq \pi - (\Gamma + \mu_1 + f(P)P)S_1.$$

Using the corresponding integrating factor, we have the following results

$$\frac{d}{dt}\left[S_1(t)\exp\left\{\mu_1 t + \int_0^t (\Gamma(\tau) + f(P(\tau))P(\tau))d\tau\right\}\right] \geq \pi\exp\{\mu_1 t + \int_0^t (\Gamma(\tau) + f(P(\tau))P(\tau))dt\right\}.$$

Integrating the above inequality results in

$$S_1(t)\exp\left\{\mu_1 t + \int_0^t (\Gamma(\tau) + f(P(\tau))P(\tau))d\tau\right\} - S_1(0) \geq \int_0^t \pi\exp\left\{\mu_1 t + \int_0^t (\Gamma(\tau) + f(P(\tau))P(\tau))d\tau\right\} dt. \quad (5.11)$$

Clearly

$$S_1(t) \geq S_{10}\exp\left\{-\left[\mu_1 t + \int_0^t (\Gamma(\tau) + f(P(\tau))P(\tau))d\tau\right]\right\} + \exp\left[-\left(\mu_1 t + \int_0^t (\Gamma(\tau) + f(P(\tau))P(\tau))d\tau\right)\right] \times \left[\int_0^t \pi\exp\left(\mu_1 t + \int_0^t (\Gamma(\tau) + f(P(\tau))P(\tau))d\tau\right) dt\right] > 0.$$

Similarly, it can be shown that $L_1, H_1, T_1, S_2, L_2, H_2$, and $T_2 > 0$, for all $t > 0$. We can therefore conclude that the solutions of (5.2)-(5.9) with initial conditions (5.10) remain positive for all $t > 0$. This completes the proof. □

5.4 Model Analysis

Note that the model presented in this chapter is an extension of the model of substance abuse presented in Chapter 3. Therefore, since the analysis involving only substance abuse has been done in Chapter 3, in this chapter we focus on the analyses involving HIV and co-existence of the two epidemics.

5.4.1 HIV only Equilibrium

We begin by considering the population with no substance abuse, but with HIV infection only. For the analysis in this subsection, we follow the procedure outlined in [4]

Proposition 5.4.1. *The model system (5.2)-(5.9) has a drug free equilibrium given by*

$$\mathbf{E}^0_{HIV} = (\hat{S}_1, 0, 0, 0, \hat{S}_2, 0, 0, 0).$$

When the population involves only HIV persons, the system of equations (5.2)-(5.9) reduces to

$$\begin{aligned} \frac{dS_1}{dt} &= \pi - \mu_1 S_1 - f(P)PS_1, \\ \frac{dS_2}{dt} &= f(P)PS_1 - \mu_2 S_2, \end{aligned} \tag{5.12}$$

where P, the prevalence rate of HIV is given by

$$P = \frac{S_2}{S_1 + S_2}.$$

We now evaluate the reproduction number of the R_0^{HIV} by linearising the second equation of (5.12) near the disease free-steady state; where $S_2 = 0$

$$\frac{dS_2}{dt} \simeq f(0)S_2 - \mu_2 S_2, \tag{5.13}$$

$$= \left(\frac{f(0)}{\mu_2} - 1\right)\mu_2 S_2. \tag{5.14}$$

The threshold number for HIV is given as $R_0^{HIV} = \frac{f(0)}{\mu_2}$. We note that

$$\frac{dS_2}{dt} \begin{cases} > 0 & \text{if} \quad R_0^{HIV} > 1, \\ \leq 0 & \text{if} \quad R_0^{HIV} \leq 1. \end{cases}$$

The system (5.12) has an equilibrium point $\hat{\mathbf{E}}_0$ given by $\hat{\mathbf{E}}_0 = \left(\hat{S}_1, \hat{S}_2\right)$. At this equilibrium point the prevalence $\hat{P}$ will be given by

$$\hat{P} = \frac{\hat{S}_2}{\hat{S}_1 + \hat{S}_2}. \tag{5.15}$$

Note that at the equilibrium point $\hat{\mathbf{E}}_0$ the equations (5.12) satisfy

$$\pi = \mu_1 \hat{S}_1 + f(\hat{P})\hat{P}\hat{S}_1, \tag{5.16}$$

$$0 = f(\hat{P})\hat{P}\hat{S}_1 - \mu_2 \hat{S}_2. \tag{5.17}$$

Using equations (5.17) and (5.15) we evaluate the steady state such that

$$\hat{S}_1 = \frac{\pi(1-\hat{P})}{\mu_1(1-\hat{P}) + \mu_2\hat{P}}, \quad \hat{S}_2 = \frac{\pi\hat{P}}{\mu_1(1-\hat{P}) + \mu_2\hat{P}}. \tag{5.18}$$

If we combine the equations (5.17) and (5.15), we obtain

$$f(\hat{P})(1-\hat{P}) = \mu_2. \tag{5.19}$$

We note that when $\hat{P} = 0$, then $f(\hat{P}) = d$ and when $\hat{P} = 1$, then the left hand side of (5.19) is zero. Thus, the left side of (5.19) is a decreasing function of $\hat{P}$ in the interval $(0, 1)$, see also [4].

5.5 The Reproduction Number for the Coinfection Model

We linearise the system (5.6)-(5.9) near the steady state when only substance abuse is prevalent. We also let

$$s_1^* = \frac{S_1^*}{N^*}, \quad l_1^* = \frac{L_1^*}{N^*}, \quad h_1^* = \frac{H_1^*}{N^*}, \quad t_1^* = \frac{T_1^*}{N^*} \quad \text{to obtain}$$

$$\begin{aligned}
\frac{dS_2}{dt} &\simeq f(0)s_1^*(S_2+L_2+H_2+T_2)+\xi_1 L_2-\Lambda S_2-\mu_2 S_2,\\
\frac{dL_2}{dt} &\simeq f(0)l_1^*(S_2+L_2+H_2+T_2)+\Lambda S_2+\xi_2 H_2-\Theta_1 L_2,\\
\frac{dH_2}{dt} &\simeq f(0)h_1^*(S_2+L_2+H_2+T_2)+\sigma_2 L_2+\xi_3 T_2-\Theta_2 H_2,\\
\frac{dT_2}{dt} &\simeq f(0)t_1^*(S_2+L_2+H_2+T_2)+\rho_2 H_2-\Theta_3 T_2.
\end{aligned}$$

We then evaluate the threshold number r_0^{HIV} when HIV is introduced in the population with substance abuse at the steady state. We use the next generation matrix method [100] where

$$\mathcal{F}_i=\begin{pmatrix} f(0)s_1^*(S_2+L_2+H_2+T_2\\ f(0)l_1^*(S_2+L_2+H_2+T_2)\\ f(0)h_1^*(S_2+L_2+H_2+T_2)\\ f(0)t_1^*(S_2+L_2+H_2+T_2)\end{pmatrix},\quad \text{and}\quad F=f(0)\begin{pmatrix} s_1^* & s_1^* & s_1^* & s_1^*\\ l_1^* & l_1^* & l_1^* & l_1^*\\ h_1^* & h_1^* & h_1^* & h_1^*\\ t_1^* & t_1^* & t_1^* & t_1^*\end{pmatrix}.$$

$$\nu_i=\begin{pmatrix} -\xi_1 L_2+\Lambda S_2+\mu_2 S_2\\ -\Lambda S_2-\xi_2 H_2+\Theta_1 L_2\\ -\sigma_2 L_2-\xi_3 T_2+\Theta_2 H_2\\ -\rho_2 H_2+\Theta_3 T_2\end{pmatrix},\quad \text{and}\quad V=\begin{pmatrix} (\Lambda^*+\mu_2) & -\xi_1 & 0 & 0\\ -\Lambda^* & \Theta_1 & -\xi_2 & 0\\ 0 & -\sigma_2 & \Theta_2 & -\xi_3\\ 0 & 0 & -\rho_2 & \Theta_3\end{pmatrix}.$$

The reproduction number r_0^{HIV} is given by

$$r_0^{\mathrm{HIV}}=\rho(FV^{-1})=f(0)(s_1^*\tau_{S_2}+l_1^*\tau_{L_2}+h_1^*\tau_{H_2}+t_1^*\tau_{T_2}),$$

such that

$$\tau_{S_2}=\frac{(1-\varepsilon_1)(\Lambda^*\Theta_2\Theta_3+\Theta_1\Theta_2\Theta_3)+\sigma_2\rho_2\Lambda^*+\sigma_2\Theta_3(\Lambda^*-\xi_2)}{(\mu_2+\Lambda^*)\Theta_1\Theta_2\Theta_3[1-\varepsilon_1-\varepsilon_2-\varepsilon_3(1-\varepsilon_1)]},$$

$$\tau_{L_2}=\frac{\xi_1\Theta_2\Theta_3(1-\varepsilon_1)+(\mu_2+\Lambda^*)[\sigma_2(1+\rho_2)+\Theta_2\Theta_3(1-\varepsilon_1)]}{(\mu_2+\Lambda^*)\Theta_1\Theta_2\Theta_3[1-\varepsilon_1-\varepsilon_2-\varepsilon_3(1-\varepsilon_1)]},$$

$$\tau_{H_2} = \frac{\xi_1(\Lambda^*(\rho_2 - \Theta_2) + \xi_2\Theta_3) + (\mu_2 + \Lambda^*)(\xi_2\Theta_2 + \rho_2\Theta_1 + \Theta_1\Theta_3)}{(\mu_2 + \Lambda^*)\Theta_1\Theta_2\Theta_3[1 - \varepsilon_1 - \varepsilon_2 - \varepsilon_3(1 - \varepsilon_1)]},$$

$$\tau_{T_2} = \frac{(\xi_2\xi_3 - \xi_3\Lambda^* + \xi_1\Theta_2) + (\mu_2 + \Lambda^*)(\xi_2\xi_3 - \sigma_2\xi_2 + \xi_3\Theta_1 + \Theta_1\Theta_2)}{(\mu_2 + \Lambda^*)\Theta_1\Theta_2\Theta_3[1 - \varepsilon_1 - \varepsilon_2 - \varepsilon_3(1 - \varepsilon_1)]},$$

where $\varepsilon_1 = \frac{\xi_3\rho_2}{\Theta_2\Theta_3}$, $\varepsilon_2 = \frac{\sigma_2\xi_2}{\Theta_1\Theta_3}$, $\varepsilon_3 = \frac{\xi_3\Lambda^*}{\Theta_1(\mu_2+\Lambda^*)}$. The term ε_1 shows the probability of moving from one of L_2 and H_2 to the other and back again. The expressions τ_{S_2}, τ_{L_2}, τ_{H_2} and τ_{T_2} in the linearised model can be interpreted as life expectancies. For example τ_{S_2} is the life expectancy of an individual from the moment that person enters state S_2. See also [4]. The terms τ_{S_2}, τ_{L_2}, τ_{H_2} and τ_{T_2} are strictly less than $1/\mu_2$. Therefore, the expected number of secondary HIV-cases initiated by an average "HIV positive" individual in a population with substance abuse epidemic is less than in the population with no substance abuse. This is because problematic substance abuse reduces the average time an individual spends in a particular compartment drug related removal.

Similarly, the endemic steady state of HIV can be invaded by substance abuse. We now linearise the equations (5.3), (5.4), (5.5), (5.7), (5.8) and (5.9) near $(\hat{S}_1, 0, 0, 0, \hat{S}_2, 0, 0, 0)$ and set

$$\hat{N} = \hat{S}_1 + \hat{S}_2, \quad \hat{s}_1 = \frac{\hat{S}_1}{\hat{N}}, \quad \hat{s}_2 = \frac{\hat{S}_2}{\hat{N}} = \hat{P}.$$

Then we obtain

$$\begin{aligned}
\frac{dL_1}{dt} &\simeq \beta(L_1 + L_2 + \eta_1(H_1 + \phi_1 H_2) + \eta_2(T_1 + \phi_2 T_2))\hat{s}_1 + \gamma_2 H_1 - Q_1 L_1 - f(\hat{P})\hat{P}L_1,\\
\frac{dH_1}{dt} &\simeq \sigma_1 L_1 + \xi_1 T_1 - Q_2 H_1 - f(\hat{P})\hat{P}H_1,\\
\frac{dT_1}{dt} &\simeq \rho_1 H_1 - Q_3 T_1 - f(\hat{P})\hat{P}T_1,\\
\frac{dL_2}{dt} &\simeq \beta(L_1 + L_2 + \eta_1(H_1 + \phi_1 H_2) + \eta_2(T_1 + \phi_2 T_2))\hat{s}_2 + f(\hat{P})\hat{P}L_1 + \xi_2 H_2 - \Theta_1 L_2,\\
\frac{dH_2}{dt} &\simeq f(\hat{P})\hat{P}H_1 + \sigma_2 L_1 + \xi_3 T_2 - \Theta_2 H_2,\\
\frac{dT_2}{dt} &\simeq f(\hat{P})\hat{P}T_2 + \rho_2 H_2 - \Theta_3 T_2.
\end{aligned}$$

Then the reproduction number r_0^{sub} for substance abuse when introduced in the population

in which HIV is endemic is the spectral radius of the matrix $\mathbf{NM}^{-1}$, for

$$\mathbf{N} = \begin{pmatrix} \hat{s}_1 & \eta_1\hat{s}_1 & \eta_2\hat{s}_1 & \hat{s}_1 & \eta_1\phi_1\hat{s}_1 & \eta_2\phi_2\hat{s}_1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \hat{s}_2 & \eta_2\hat{s}_2 & \eta_1\phi_1\hat{s}_2 & \hat{s}_2 & \eta_2\hat{s}_2 & \eta_2\phi_2\hat{s}_2 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\mathbf{M} = \begin{pmatrix} \mathcal{Q}_1 & -\gamma_2 & 0 & 0 & 0 & 0 \\ -\sigma_1 & \mathcal{Q}_2 & -\xi_1 & 0 & 0 & 0 \\ 0 & -\rho & \mathcal{Q}_3 & 0 & 0 & 0 \\ -\mathcal{G} & 0 & 0 & \Theta_1 & -\xi_2 & 0 \\ 0 & -\mathcal{G} & 0 & -\sigma_2 & \Theta_2 & -\xi_3 \\ 0 & 0 & -\mathcal{G} & 0 & -\rho_2 & \Theta_3 \end{pmatrix},$$

where $\mathcal{Q}_1 = Q_1 + f(\hat{P})\hat{P}$, $\mathcal{Q}_2 = Q_2 + f(\hat{P})\hat{P}$, $\mathcal{Q}_3 = Q_3 + f(\hat{P})\hat{P}$ and $\mathcal{G} = f(\hat{P})\hat{P}$. The resulting characteristic polynomial yields two distinct eigenvalues, of which the maximum is the expression of r_0^{sub}. Whether the magnitude of r_0^{sub} is greater or smaller than R_0 in Chapter 3 depends on the parameter values chosen. The coinfection model is complicated to deduce reasonable analytical results, thus we resort to numerical simulations.

5.6 Numerical Simulation

We carry out numerical simulation to determine the behaviour of population of drug users and the trend of HIV among the drug using populations. We estimate some of the parameters to be used in the numerical simulations and detail them in Table 5.4. The demographic parameters μ_1 and μ_2 are specific to the sub- Saharan region. The parameter $\mu_2 = 0.1$per year correspond to the life expectancy of 10 year for the HIV infected individuals [4] and the references therein. However, this value can be higher or smaller $(8 - 20$ years) depending on the nutrition and life style of these individuals.

Parameters d, λ *and* t_0; To estimate these HIV related parameters we follow the method used in [4]. This is feasible because similar data is used to estimate these parameter.

These parameters are necessary and usually sufficient to fit any set of increasing numbers resembling the logistic curve [4]. We use data for prevalence of HIV infection in a peri-urban community in the Western Cape province of South Africa 1996 – 2004, to fit the model to data and derive the specific parameters. The HIV prevalence data obtain from [4, 52] is indicated in Table 5.3.

Year	1996	1997	1998	1999	2000	2001	2002	2003	2004
Pop'n Size	5518	6429	7339	8250	9161	10,071	10,982	11,892	12,803
HIV Prev(%)	6.3	8.9	11.6	14.2	16.5	18.4	19.9	21.1	21.9
Est. HIV + people	348	572	851	1172	1512	1853	2185	2509	2804

Table 5.3. HIV prevalence in a peri-urban community in the Western Cape.

We sum the first four equations (5.2)-(5.5) for HIV− people and the four equations (5.6)-(5.9) for HIV+ people. Setting $X_1 = S_1 + L_1 + H_1 + T_1$ and $X_2 = S_2 + L_2 + H_2 + T_2$ and taking the prevalence to be $X = \frac{X_2}{X_1+X_2}$, we obtain

$$\frac{dX_1}{dt} = \pi - \mu_1 X_1 - f(P)PX_1 - \delta_1 H_1 - (d_1 + k_1)T_1, \tag{5.20}$$

$$\frac{dX_2}{dt} = f(P)PX_1 - \mu_2 X_2 - \delta_2 H_2 - (d_2 + k_2)T_2. \tag{5.21}$$

To estimate the parameters d, λ and t_0, we assume that the terms involving H_1, T_1, H_2 and T_2 form a very small proportion of the drug using population and therefore ignore them. The resulting system is in terms of X_1 and X_2. If we take the base year for the for the onset of HIV to be $t_0 = 1980$, then we have; $X_1(t_0) = \frac{\pi}{\mu_1}$ and $X_2(t_0) = 1$.

The parameter values entered in the Table 5.4 are estimated values per year.

Parameter	Range	Value	Source	Parameter	Range	Value	Source
β		0.3	fitted	γ_3	0.3-0.5	0.45	fitted
η_1	0-1	0.6	fitted	ξ_1	0.1-0.4	0.18	fitted
η_2	0-1	0.4	fitted	ξ_2		0.24	fitted
ϕ_1	0-1	0.3	fitted	ξ_3		0.4	fitted
ϕ_2	0-1	0.25	fitted	ρ_1	0.17-0.3	0.23	fitted
π		400	fitted	ρ_2	0.17-0.4	0.3	fitted
μ_1		0.02	[1]	δ_1		0.0028	fitted
μ_2	(0.05-0.125)	0.1	[4]	δ_2		0.0028	fitted
σ_1	0.2-0.6	0.3	fitted	d_1		0.0014	fitted
σ_2	0.2-0.6	0.5	fitted	d_2		0.0038	fitted
γ_1	0.3-0.5	0.25	fitted	k_1	0.1-0.5	0.45	fitted
γ_2	0.3-0.5	0.28	fitted	k_2	0.2-0.5	0.3	fitted
d	0.48-0.50	0.49	fitted	λ	5.3-5.8	5.6	fitted

Table 5.4. Parameter values used in model simulations

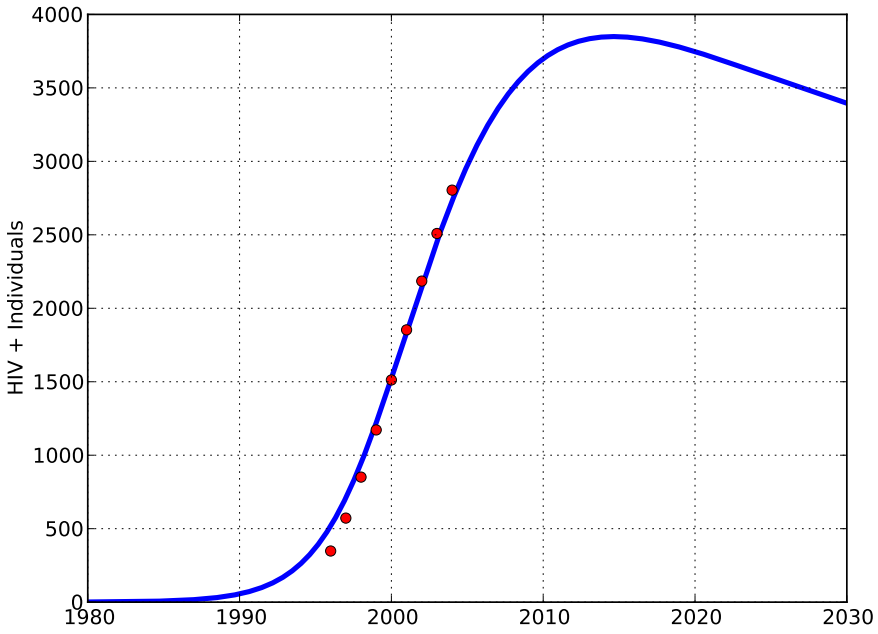


Figure 5.2. A graphical representation of the HIV positive population from the model (5.2)-(5.9) fitted to data for HIV positive individuals in Table 5.3

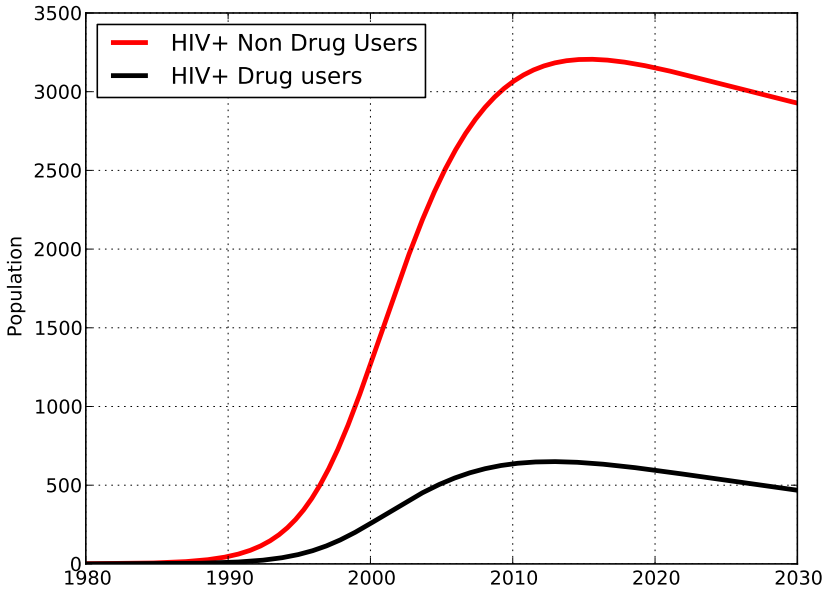


Figure 5.3. Variation of the population of HIV positive non drug users and the population of HIV positive drug users.

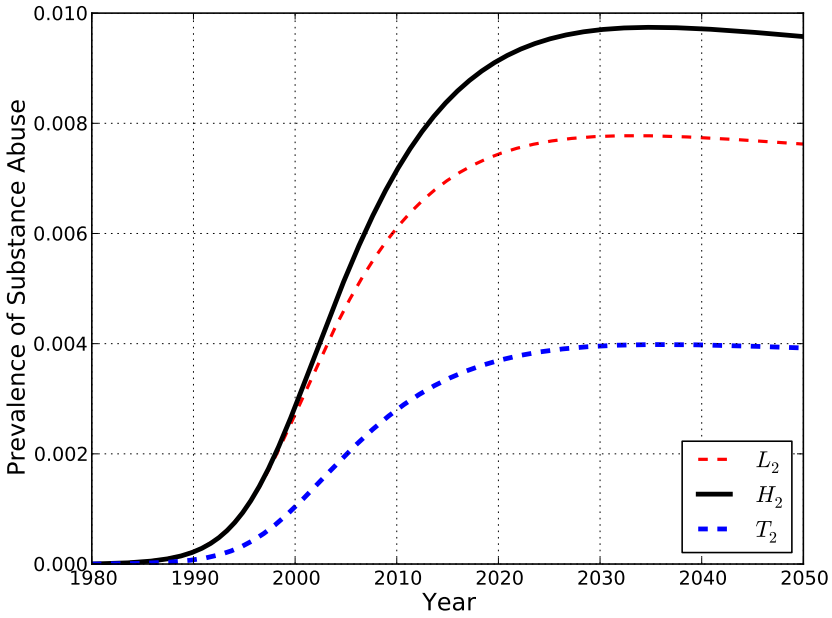


Figure 5.4. Prevalence of substance abuse among HIV infected individuals.

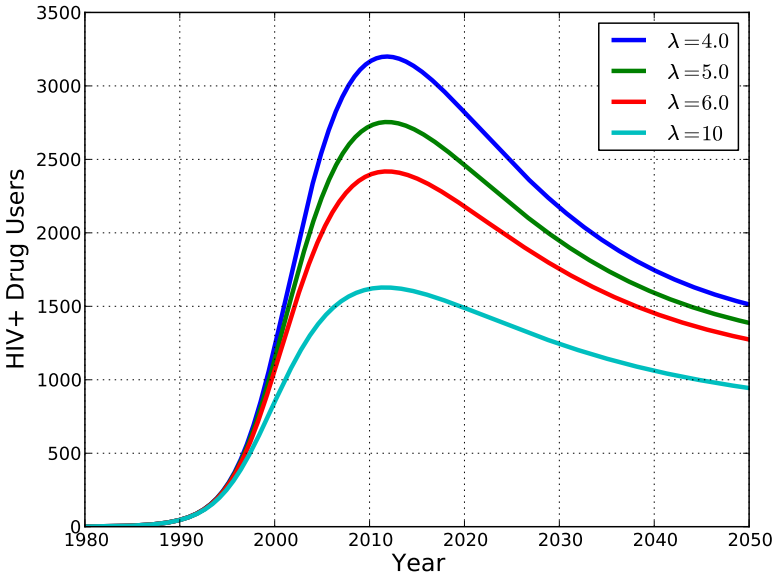


Figure 5.5. Impact of the speed at which information about HIV spreads on the prevalence of HIV among drug users.

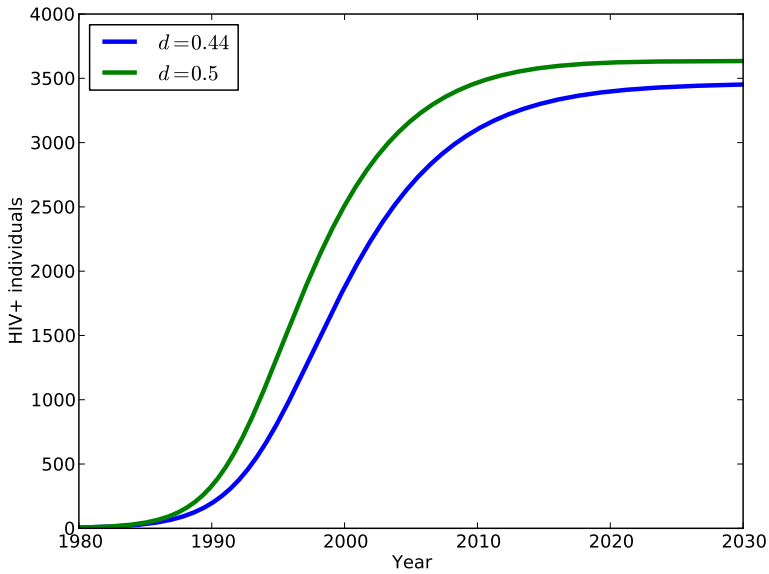


Figure 5.6. Effect of sexual hyperactivity and other local cofactors on the prevalence of HIV.

5.7 Summary

The simulation results in Figure 5.2, show the mathematical model fitted to the HIV prevalence data in Table 5.3 from a peri-urban community in the Western Cape. The parameter values used for the model simulation are as indicated in Table 5.4. Information dissemination is an important component in the control of epidemics associated with human behaviour. We observe that increasing the spread of information about HIV, Figure 5.5, reduces the prevalence of HIV among drug users. This is mainly due to change in behaviour, for example, injecting drug users resorting to smoking drugs in the case of HIV. Our simulations show that the unprecedented increase in both drug use and spread of HIV occurred in the mid $1990's$. Our results suggest that most individuals who start using substances end up becoming drug dependent, and if no control measures are taken, in the long run every four of ten drug dependent HIV positive individuals will require treatment/rehabilitation related to substance abuse. This consequently has worse implications on the efficacy of antiretroviral therapy and adherence to it, CD4 cell count and immuno modulation among drug dependent HIV seropositive individuals. Heavy alcohol consumption and drug addiction are associated with sexual hyperactivity and increased sexual contact increases the risk of contracting HIV. Our results in Figure 5.6 suggest that, there is faster spread of the HIV epidemic and high prevalence with increased sexual contact.

Chapter 6

Conclusion and Discussion

In this thesis, we studied the general substances abused, highlighting those abused heavily, moderately and to a low extent. With specific reference to heavily abused drugs, we highlighted the modes of administration of such drugs, the time at which peak plasma concentrations are reached and the general health effects associated with each of the drugs considered. In addition, we considered the factors that account for the spread of drug epidemic as well as factors responsible for its reduction.

In this study we presented two models on substance abuse and one model on the relation between substance abuse and HIV/AIDS. The first model presented in Chapter 3, describes the dynamics of substance abuse based on the assumption that drug users behave as diseased individuals and that a susceptible individual meets only a fraction drug users. The model incorporates key aspects such as recruitment into rehabilitation, relapse at a constant rate, amelioration and quitting of light drug users in addition to interaction (contact) between drug users and the susceptible population. This model was extended in Chapter 4 to incorporate a compartment of drug lords as the main drug supply chain. The main interest here was to investigate the contribution of drug lords in drug epidemics and the impact of law enforcement on the prevalence of substance abuse. Our results indicate that; the presence of drug lords increases the prevalence of substance abuse. On the other hand, law enforcement reduces the population of drug suppliers and consequently the prevalence of substance abuse. In Chapter 5, a model incorporating the possibility of drug users contacting HIV was presented. This transition from HIV-negative to HIV-positive state is associated with behavioural change, drug use patterns, sexual life style and response

to information dissemination regarding HIV/AIDS. Qualitative and numerical analyses of all the above mentioned models was done.

Mathematical analysis of the model with amelioration, Chapter 3, indicates that there exists a drug free steady state which is globally stable whenever $R_0 < 1$ and a unique drug persistent steady state which is globally stable when $R_0 > 1$. The epidemiological interpretation of this being that, substance abuse can be eliminated if the reproduction number is reduced to a value below unity. The importance of model parameter to the prevalence and spread of drug epidemics was investigated using the normalised forward sensitivity indices with respect to the reproduction number. This sensitivity analysis together with the numerical simulations consistently show that prevalence of substance abuse increases with increase in the influence (contact) of drug users on the susceptible population, re-initiation (relapse or reversion) into drug use and amelioration in the absence of quitting for light users. On the other hand, prevalence of substance abuse reduces with increase in recruitment into rehabilitation, and with amelioration in presence of quitting for light users. Analysis of the model involving drug lords indicates existence of a globally asymptotically stable steady state whenever $R_{0UD} < 1$ and a possibility of two endemic equilibria when $R_{0UD} > 1$. We note that, at all times $R_0 < R_{0UD}$. Therefore, the contribution of drug lords in drug epidemics is significant and can not be overlooked. The numerical results indicate that effective interaction between drug lords and potential drug users increases the prevalence of substance abuse whereas increased law enforcement reduces the prevalence of substance abuse.

In order to understand the potential impact of substance abuse on the prevalence of HIV/AIDS, we formulated a model with maximum transmissitivity and dissemination of information on HIV/AIDS among drug users. Our analysis suggests that in absence of substance abuse, HIV can be eliminated if R_0^{HIV} is reduced below unity. Otherwise, it remains prevalent. We observed that, increasing the spread of HIV/AIDS related information in the population directly reduces the prevalence of the epidemic.

In this research, we were able to understand the drugs abused, and the key factors that influence the dynamics of substance abuse. We were also able to identify the key target parameters for controlling drug epidemics and consequently HIV/AIDS. Our recommendation for further research on this topic are as follows:

1. The fact that different age groups have different drug using patterns, it is important to structure the population into different age groups. This may help researchers and policy makers to;
   - assess the demographic impact of drugs with significant morbidity and mortality.
   - estimate parameters related to drug use patterns from age-specific data.
   - design control and intervention programs to protect vulnerable age groups.
2. Data on the numbers of drug users should be collected, for each specific drug accounting for multiple drug usage. This data will be important in looking for synchrony of drug epidemics over the different provinces and possible periodicity in drug use patterns.

All these will help in better understanding of drug use patterns and designing proper control and rehabilitation strategies.

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